# SURGERY

VOL. 3 JANUARY, 1938 NO. 1

## Original Communications

### THE OPERATIVE TREATMENT OF SCARS FOLLOWING BEDSORES

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#### INTRODUCTION

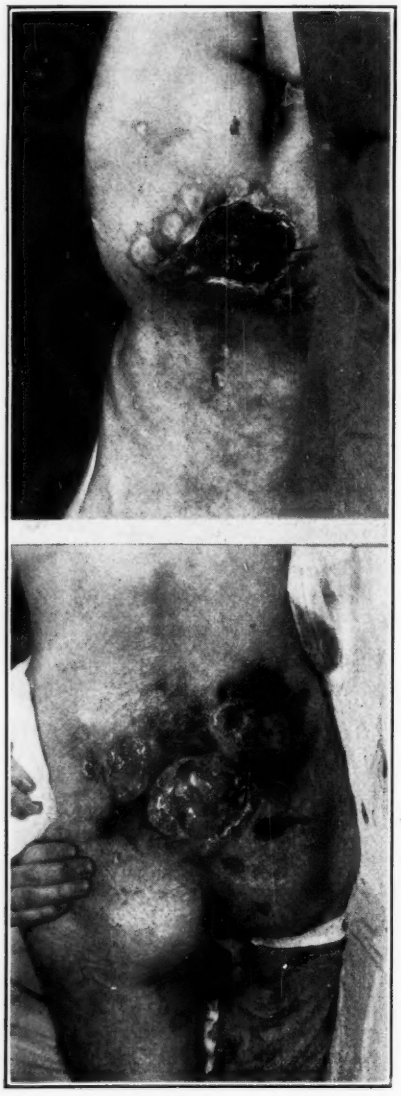
THE subject of decubitus, pressure ulcers, or bedsores, as you may choose to call them, is of definite interest to every physician or surgeon who has under his care patients who are confined to bed over long periods of time.

The prevention of the formation of bedsores in either obese or emaciated patients who are bedridden, and who are unable because of injury or disease to move themselves or to be moved satisfactorily, is a very difficult matter. In these cases, tissue destruction due to pressure occurs quite frequently over the bony prominences where they rest on the mattress, and sometimes in spite of the most vigilant and skillful nursing bedsores develop with great rapidity. This is especially liable to occur in those instances where in addition to the pressure factor there is incontinence of feces or urine. The tissue destruction frequently includes all of the soft parts over the underlying bone.

It is needless to say that every effort should be made during the treatment of these patients to build them up with transfusions and all other necessary procedures. As the general physical condition improves, these ulcers, which may be very large and which are always infected, will eventually heal slowly. Even if it is possible to hasten the healing with dressings of various kinds, or by the use of buried skin grafts which are sometimes successful, the final result is, as a rule, a thin unstable scar which is closely adherent to the bone. The circulation in these thin scars is very poor, and the bone is close to the surface; so in those instances where the patient is still confined to

Received for publication, May 5, 1937.

bed after the unstable healing has taken place, the weight of the body on the scar, in spite of every precaution to avoid pressure, will cause further necrosis of the scar and chronic ulceration, which is often very painful.



*B.*

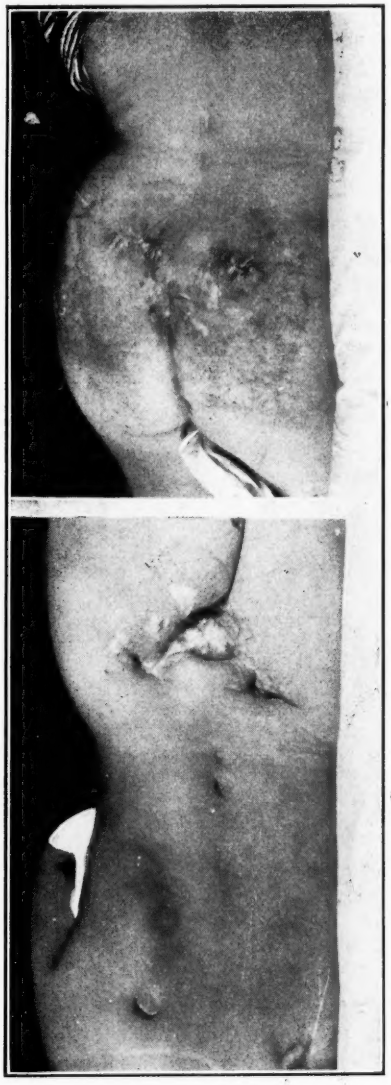
*A.*

Fig. 1*A* and *B*.—Illustrating the type of bedsore which occurs in a bedridden emaciated patient. An eleven-year-old girl was severely injured and also seriously burned in an automobile accident and on account of her precarious condition could not be moved. There was also incontinence of feces and urine. She became much emaciated; bedsores developed. *A*, shows the condition of the lumbosacral region four months after the accident, at which time she came under the author's care. Note the multiple ulcerations and the unhealthy condition of the surrounding skin. *B*, Six months later. During four months of this period the condition of the patient was grave, then the patient's general condition improved considerably and definite healing can be noted. Healing was complete one year after admission, and the patient's general condition was much improved. The thin scar breaks down from time to time.

The scars vary in shape and size, but frequently they conform roughly to the outline of the sacrum. They are usually sharply depressed in regard to the surrounding soft parts, which bulge up from or even overhang the tightly adherent scar margins.

The purpose of this communication is to call attention to a simple method of relieving this troublesome condition, which may cause a

great deal of discomfort to the bedridden patient and which also may prevent necessary operative work on neighboring parts on account of the danger of infection from the chronic ulceration. My remarks are based largely on the treatment of scars in the lumbosacral region, as



*D.*

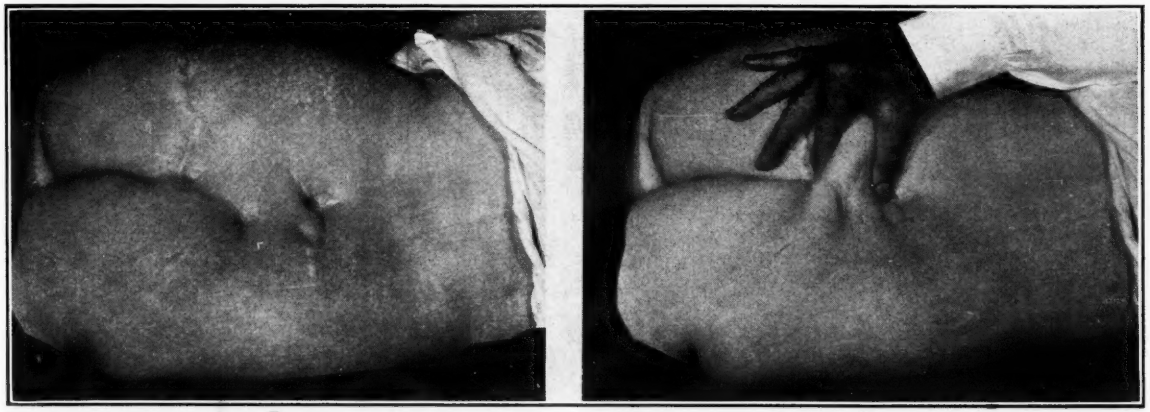
*C.*

Fig. 1*C* and *D*.—*C*, The depressed unstable scar about two years after admission. The patient has been continuously bedridden during this period. Note the improved condition of the surrounding skin and the increase in weight. *D*, Three weeks after the excision of the unstable scar and closure by undercutting and shifting flaps of skin and subcutaneous tissue. This result has been permanent for two years, and although the patient has been continuously confined to bed on account of bilateral ankylosis of the hip joints and other lesions, there has been no sign of breakdown since the operation.

this is the most common location. The problem is to bring about a stable comfortable healing; in order to accomplish this, it is essential to substitute for the thin unstable scar a thick resistant mass of whole thickness skin and subcutaneous tissue. I have been using the following procedure for a number of years with satisfaction and others also may have used the same general method.

*A.* *B.*

Fig. 2*A* and *B*.—Illustrating the type of scar which followed a bedsore on an obese individual. A forty-two-year-old woman had puerperal septicemia two years before admission. The left hip joint became involved and ankylosis followed. An extensive bedsore developed. Several unsuccessful skin graftings were done elsewhere during the slow healing process and an unsuccessful plastic operation was also performed. The patient was permanently bedridden on account of the ankylosis of the hip joint, but nothing could be done to relieve the ankylosis until a permanent healing of the unstable scar over the sacrum was accomplished. *A*, Note the size and irregular shape of the tightly adherent scar and also the areas of ulceration. The tissues immediately adjacent are more or less infiltrated with scar. *B*, Two months after excision of the scar and closure of the defect with broad pedicled flaps of skin and subcutaneous tissue formed from adjacent tissue by undercutting plus relaxation incisions and adjusted to cover the defect. Note the irregularity of the closure and the thick pad of tissue which has replaced the scar. The patient was bedridden for one year longer and was then operated on to relieve the hip ankylosis. Closure has been permanent.



*C.* *D.*

**Fig. 2*C* and *D*.—Photographs taken five years after repair by the method described. The patient is up and about and has had no further trouble. Compare the scar with the photographs taken two months after operation. Note the thick, freely movable tissue which covers the old scar area.**

In preparation for the operation, an attempt is made to clean up the ulcerated area until the bacterial count is satisfactory, by any means which has proved effective in the hands of the surgeon. A local anesthetic may be used, but my preference in these cases is for avertin-nitrous oxide-oxygen anesthesia. The ulcerated area is thoroughly carbolized, and the skin is carefully cleaned up with ether, alcohol, and potassio-mercuric-iodid (Kalmarid), 4 gm. in 460 cm. of acetone. The thin scar area is completely excised and the thick surrounding tissue is freely mobilized as far back as is necessary. The margins are trimmed and all bleeding is checked. The mobilized tissue consists of the whole thickness of the skin with as much of the subcutaneous fat as is desired. Unless the scars are comparatively narrow, it may not be possible to advance these mobilized margins directly so that they may be sutured over the defect without tension. In many instances, it is essential to make suitable relaxing incisions completely through the undermined tissues, and these incisions, which may be either transverse or oblique or angled, are placed so as to form what may be roughly designated as wide single pedicled flaps. In order to cover the defect, these flaps are either advanced or transposed as the case may be and are adjusted so that they may be sutured together without tension. It is not possible to give accurate directions as to the placing of the incisions and the formation of the flaps, as each case is a law unto itself. After mobilization and formation of the flaps, the subcutaneous tissue margins are brought in approximation with catgut sutures. The skin is closed with on-end mattress sutures of horsehair, alternating with similar sutures of black waxed silk. If drainage is necessary, a few strands of horsehair may be inserted under the flaps, the ends emerging between two of the sutures. These strands are left long and are so arranged that they may be withdrawn in twenty-four to forty-eight hours without disturbing the rest of the dressing. A single thickness of gauze impregnated with 3 per cent xeroform ointment is placed over the suture line and over this a few layers of gauze and a thick sterile seasponge which has been thoroughly wrung out. More gauze is placed over the sponge, and the dressing is secured with long wide strips of adhesive plaster, which exert enough pressure to obliterate all dead spaces, and over this is placed a sung Scultetus bandage. The patient is kept in the prone position or on the side, but if it becomes necessary to turn on the back, the wound is protected by a circular or horseshoe-shaped air cushion or by pads arranged to prevent pressure. The sutures are gradually removed as they loosen, and the wound is protected by gauze pads held by adhesive plaster for several weeks longer. Except in the simpler cases where the edges, after mobilization, can be ap-

proximated in a straight line, the closure is often found to be in irregular lines, as can be seen by observing the closed wounds in the two cases used for illustrating these scar types.

Inasmuch as there is often, in the acute stages of the breakdown, extensive undermining of the surrounding tissues as well as some surface destruction, we frequently find after healing has taken place that the tissues adjacent to these depressed scars are more or less infiltrated with scar. For this reason, it is advisable to delay operative closure for several months until these tissues can be softened and loosened by systematic massage. If the shifting is done before this loosening is accomplished, the result is usually a total failure.

I have been asked why the same result cannot be accomplished with free grafts. The answer is that if free skin grafts could be successfully transplanted after excision of the scar on a base with such poor circulation, the result would not be sufficiently resistant, on account of its lack of subcutaneous padding, to bear the body weight over any prolonged period without breakdown, if the patient is still bedridden.

The method may also be used successfully in dealing with adherent unstable and painful scars following bedsores over the scapulae and other bony prominences on the trunk. Tissue destructions over bony prominences on the extremities due to pressure may have to be handled by other measures, such as skin grafting or flaps from a distant part, if there is scarcity of adjacent shiftable tissue.

## CONCLUSIONS

The procedure described in this paper will, after healing is complete, allow the bedridden patient to lie on his back with safety and comfort, as the pad of whole thickness skin and subcutaneous fat which has been shifted in to fill the defect is thicker than the original normal tissue and adequately covers the bony prominences. The nerve supply in the shifted tissue is usually not seriously disturbed and the resistance of this tissue is sufficiently great to prevent further breakdown. The procedure is simple. Adjacent tissues are utilized and are sutured without tension. A stable painless healing is the result.

# ACROMEGALY

## A Detailed Report on Two Cases

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ALL cases of acromegaly showing points of interest are worthy of recording, and for this reason we have ventured to publish the two following cases:

Case 1.—I. W. came under observation in September, 1930, at the age of twenty-one years, complaining of constant headaches and pains in her neck which had been present for nine months. Two years previously she suffered from a bad attack of influenza which was followed by intermittent headaches. She put on weight gradually and noticed that her lower jaw was getting larger and causing her some difficulty in deglutition.

On admission to hospital on September 30, 1930, the patient was found to be very irritable and suffered from thirst and polyuria. There was no enlargement of the thyroid gland or deformity of the spinal column. Her blood sugar curve was normal. Wassermann reaction in blood and cerebrospinal fluid was negative. Menses were very irregular. The patient was somewhat somnolent and was often found to be sound asleep during the day. She had a good crop of hair which showed no tendency to fall out. The urine was normal on the many occasions on which it was examined. There was some papilledema of both disks. The veins were full (see charts). Vision was as follows:

Right vision 6/9
Left vision 6/9
Visual fields somewhat constricted (see charts)

Skiagram revealed a large pituitary fossa. Her weight was 12 stone 9 pounds (177 pounds). Blood pressure was 118/80.

Her hands and feet were considerably enlarged; she took size eight in shoes. As the headaches became worse and the patient had some occasional attacks of vomiting, it was decided to operate and to insert some radon seeds into the pituitary fossa.

On November 7, 1930, under intratracheal ether anesthesia and local infiltration of the scalp, an ear-to-ear incision was made and the large anterior flap turned forwards over the face. A large osteoplastic flap was raised over the right frontal lobe and hinged outwards on the anterior fibers of the temporal muscle. The dura mater was then carefully raised from the anterior fossa of the skull as far as the lesser wing of the sphenoid bone. The dura mater was incised and an illuminated retractor inserted, when a large pituitary tumor was exposed. A small piece was removed for section and nine radon seeds inserted into the tumor. The dura mater was allowed to fall back into position and the bone flap returned and sutured. The scalp was united with interrupted sutures and the patient returned to the ward in good condition. Recovery was uneventful, and the patient was discharged on December 30, 1930. She was kept under close observation.

Received for publication, July 17, 1937.

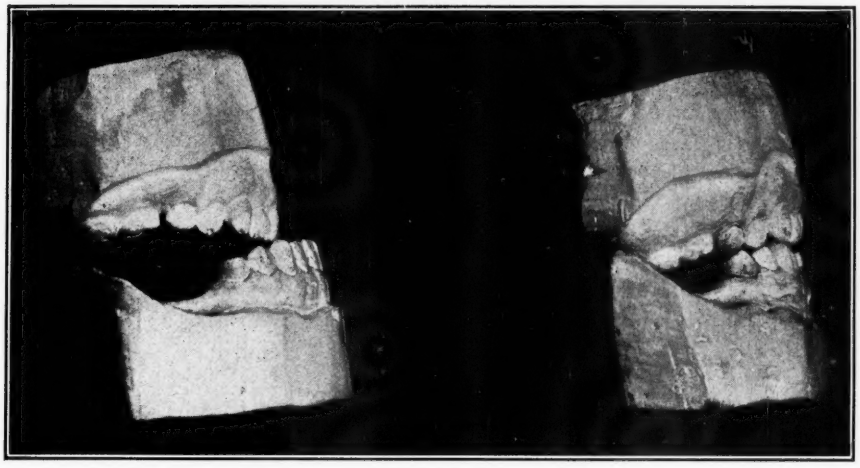

Fig. 1.—Photograph showing the bite of the patient—left, before operation; right, after operation.

Fig. 2.—Photograph of patient after resection of the lower jaw, showing the normal contour of the face.

The papilledema, polyuria, and headaches completely disappeared, but the difficulty in mastication, which was present before operation, persisted, and her tongue always seemed too large for her mouth. There was no doubt whatever that the growth of her enlarged bones, jaws, hands, and feet had remained unchanged since the operation. Because of the imperfect occlusion of the teeth, due to the enlargement of the mandible (Fig. 1), it was decided to remove portions of the mandible on each side, together with a V-shaped portion of the tongue. The visual acuity and fields of vision were normal.

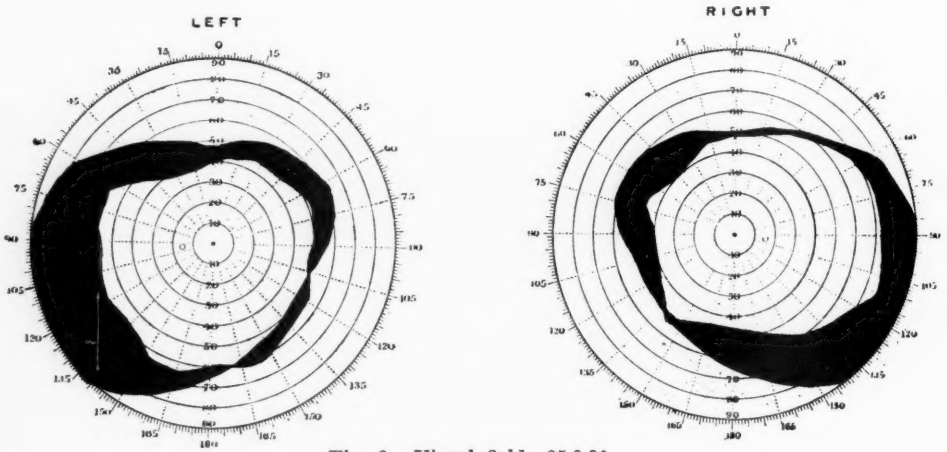


Fig. 3.—Visual fields 25.9.30.

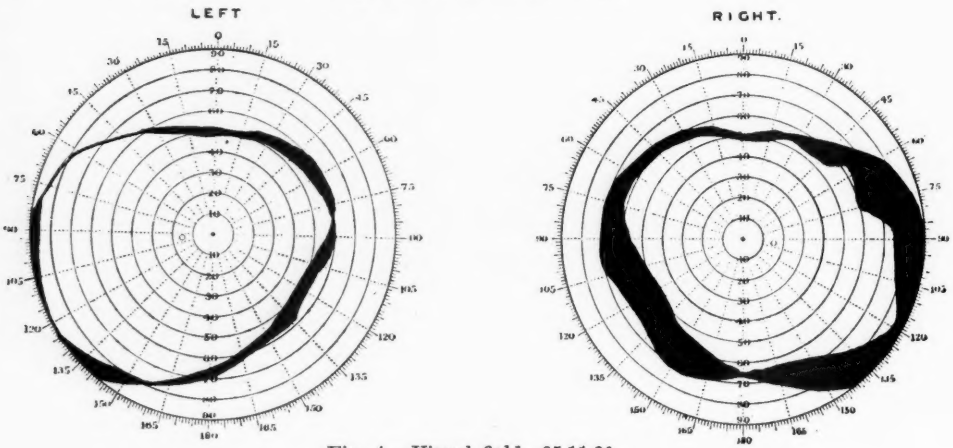


Fig. 4.—Visual fields 25.11.30.

On October 26, 1934, four years after the previous operation, under avertin, and gas and oxygen anesthesia, a V-shaped incision was made into the anterior portion of the tongue, and the anterior third removed, the raw surfaces being united with interrupted sutures. The mucoperiosteum was then raised from the middle of the horizontal ramus on each side and a large wedge-shaped portion of bone removed. Bleeding was controlled by pressure and a four-tail bandage applied to the jaw. Excessive salivation after the operation was treated with injections of atropine and discontinuous suction drainage.

On November 16, 1934, a silver double cup splint was applied over the teeth in the lower jaw and kept in position for six weeks. A small abscess formed below the lower jaw, but this was opened and drained and healed readily. (Fig. 2.)

The patient was discharged on February 12, 1935, when firm union of the bone was present. She was readmitted on November 1, 1935, for the extraction of a right mandibular third molar which was erupting badly. Her general condition was excellent; she no longer suffered from headaches or had any difficulty in reading. She was working as a domestic and has been ever since.

*Remarks.*—Owing to the excessive enlargement of the tongue and the marked prognathism, it was considered advisable to remove a piece of the mandible and to perform a partial glossectomy with the excellent result shown in Fig. 1.

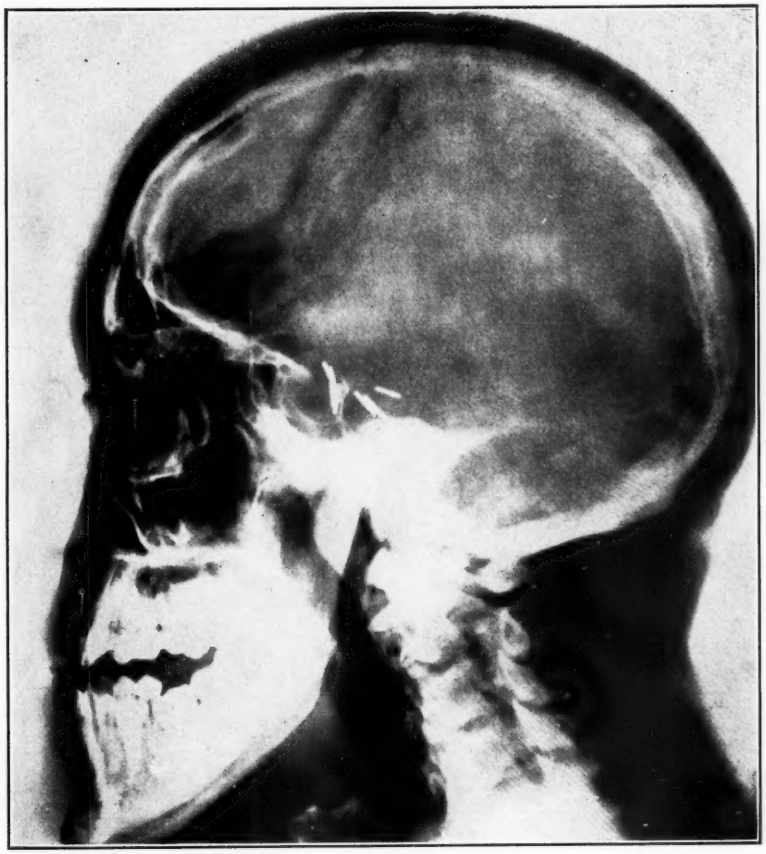

Fig. 5.—Lateral skiagram of skull showing position of radon seeds in situ.

Hypertrophy of the tongue is the most frequent symptom met with in acromegaly after the enlargement of the bones. Of the 726 cases in which the condition of this organ is mentioned, hypertrophy is described in 689 cases (94.5 per cent); it was normal in 35 cases and said to be small in 2, but in 1 of these it was stated, in one part of the description of the case, to be small, and in another to be normal (Tanzi). Removal of a part of the lower jaw in order to improve the bite has only been reported once before (Blessing and Rost), and here again the result was excellent. There was no enlargement of the thyroid

gland. This has been the case in 189 reports (33 per cent) out of 573 cases recorded. In 250 cases, the gland was found to be enlarged (44 per cent) and in the remaining 134 cases various conditions are described.

*Spinal Column.*—It is unusual, as in this case, to find no alteration in the spinal column. A change of some kind or other is the third commonest symptom in acromegaly. The condition of the spinal column has been described in 598 cases; it was normal in 99 cases (16.6 per cent)

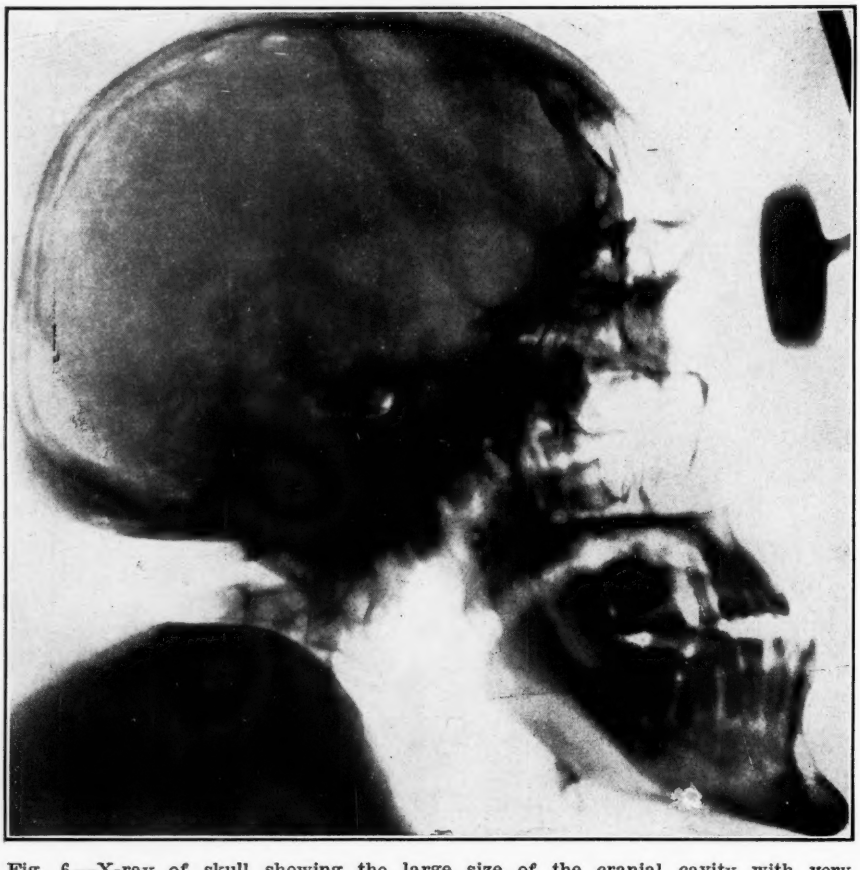

Fig. 6.—X-ray of skull showing the large size of the cranial cavity with very enlarged sella turcica.

and altered in the remaining 499 (83.4 per cent); kyphosis is the commonest condition, 360 (72 per cent), most often in the cervicodorsal region; kyphoscoliosis, 83 cases (16 per cent), and scoliosis 40 cases (8 per cent). The column was changed in some other way in 16 cases.

*Eyes.*—Some affection of the eyes is quite common in acromegaly. Of the 1,132 cases in which the condition of the vision is described, in 319 cases (28 per cent) it was normal, and in 813 (72 per cent) it was affected in some way or the other. Restriction of the visual

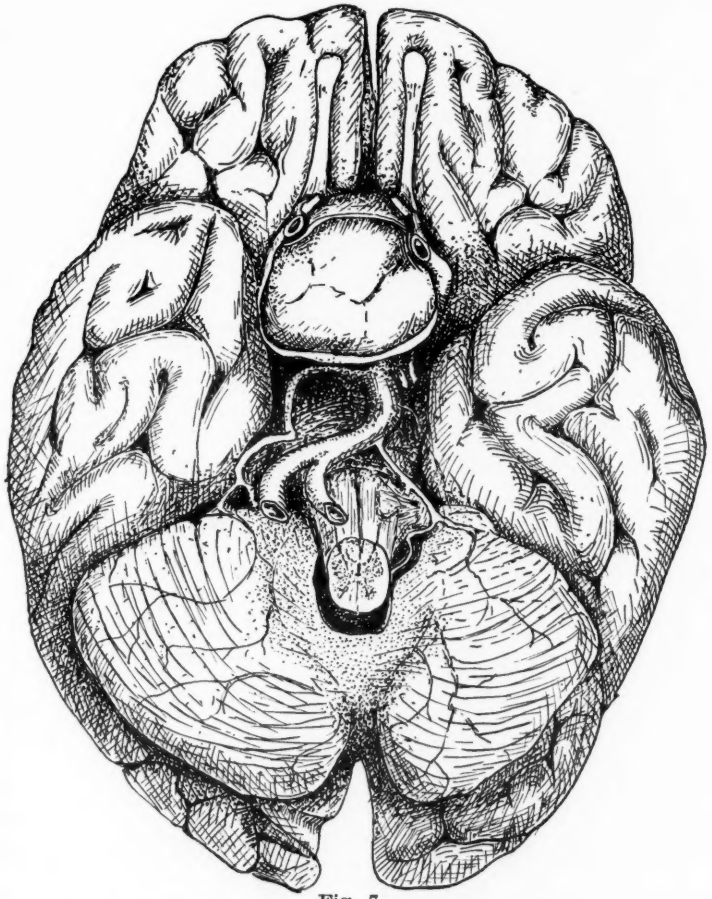

Fig. 7.

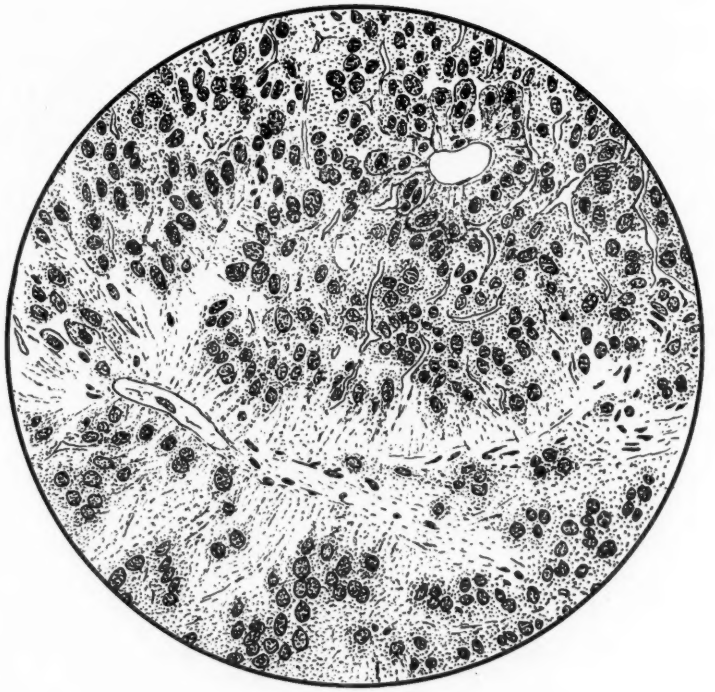

Fig. 8.

**Fig. 7.**—Drawing of the under surface of the brain showing the large pituitary gland with the thinned out optic nerves.
**Fig. 8.**—Microscopic drawing of the pituitary gland in Case 2.

Fig. 9.—Photograph of normal skull placed on the top of the skull from Case 2.

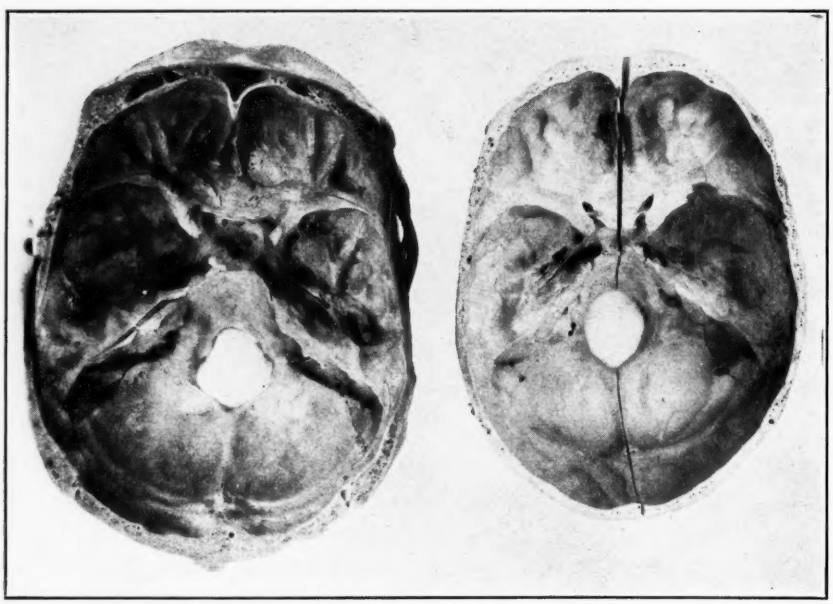

Fig. 10.—Photograph of sectioned acromegalic skull from Case 2 on the left compared with a normal skull on the right.

field, papilledema, bitemporal hemianopsia are of frequent occurrence. An examination of the charts will show the happy result from the insertion of radon seed into the pituitary gland (Figs. 3, 4, and 5). This is the first case in which this operation was performed—Bertolotti preferring to employ it endonasally. The transfrontal approach has the great advantage, as the operation is performed under the direct view of the operator.

The presence of amenorrhea, as in this case, is a common early symptom and is sometimes the first to which the patient's attention is drawn.

*Urine.*—No albumin or sugar was present in the urine. Albumin has been found in the urine in 149 (22 per cent) out of 676 cases,

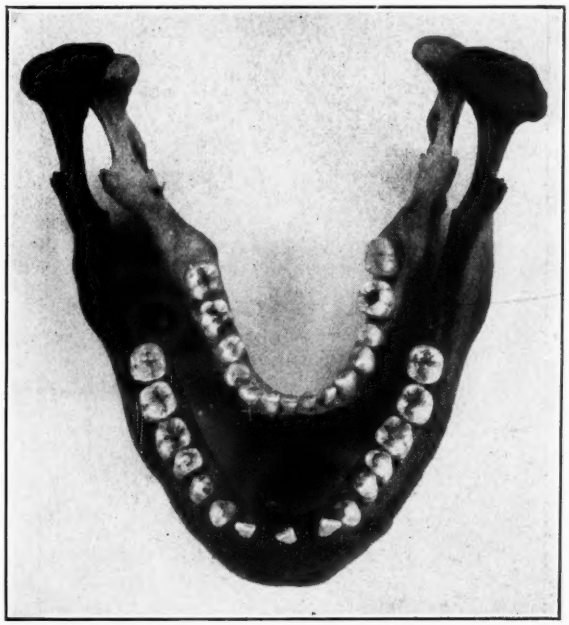

Fig. 11.—Photograph of lower jaw from Case 2, inside which is a normal mandible.

and absent in 527 (78 per cent). Sugar is more frequently discovered and in some cases is alimentary. It was present in 262 cases out of 800 (33 per cent) and absent in 538 (67 per cent).

*Sex.*—Up to the end of the year 1936, reports on 1,564 cases have been recorded: the sex is not stated in 67; of the remaining 1,497, the males amounted to 770 and the females to 727; there is therefore a slightly greater preponderance in favor of the male sex.

*Age.*—The sex and age are stated in 1,322 cases; no data being available in the remaining 242 cases. It will be seen from the following table that the commonest age for acromegaly to commence is, as in the case of the patient, between the ages of twenty-one to thirty years (503, 40 per cent).

| AGE GROUP | MEN | | WOMEN | | TOTAL | |
|---|---|---|---|---|---|---|
| | NO. | % | NO. | % | NO. | % |
| Up to 20 years | 144 | 21.7 | 83 | 12.6 | 227 | 17.2 |
| 21 to 30 years | 243 | 36.7 | 260 | 39.5 | 503 | 38.0 |
| 31 to 40 years | 166 | 25.0 | 193 | 29.3 | 359 | 27.2 |
| 41 to 50 years | 80 | 12.1 | 80 | 12.1 | 160 | 12.1 |
| Over 50 years | 30 | 4.5 | 43 | 6.5 | 73 | 5.5 |
| Total | 663 | 100 | 659 | 100 | 1322 | 100 |

CASE 2.—L. W. was the second son of a family of two. He enjoyed good health until the age of twenty-five years when he first began to suffer from frontal

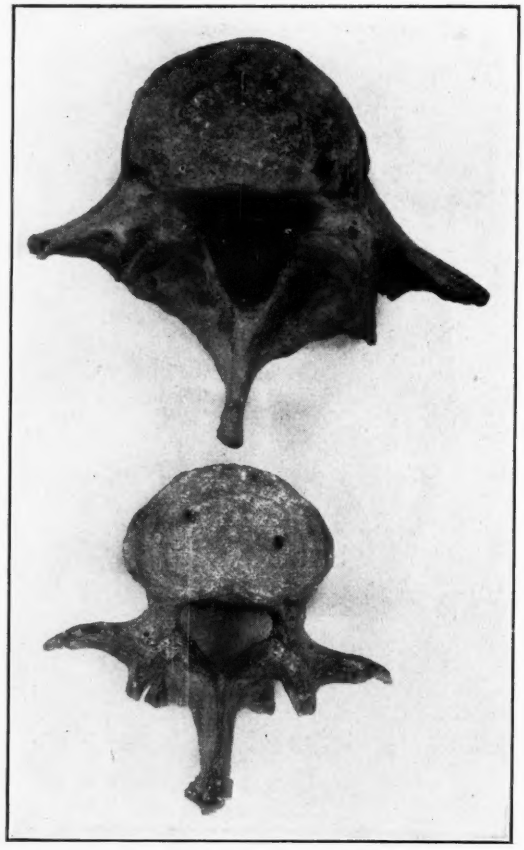

Fig. 12.—Photograph of lumbar vertebra from Case 2, compared with a normal (below).

headaches. He worked as a bank clerk and was able to continue to do so until the age of thirty-six years, when he became so tired and listless that he was obliged to give up work and retired to Brighton.

When examined at the age of twenty-five years, he was found to have early signs of acromegaly, some enlargement of the hands and feet, and an enlarged skull with considerable ballooning of the sella turcica. His urine contained sugar but no other abnormality. The visual fields were full and there was no sign of papilledema.

Fig. 13.—Right femur from Case 2 compared with a normal femur. There are advanced osteoarthritic changes in the lower end of the femur.

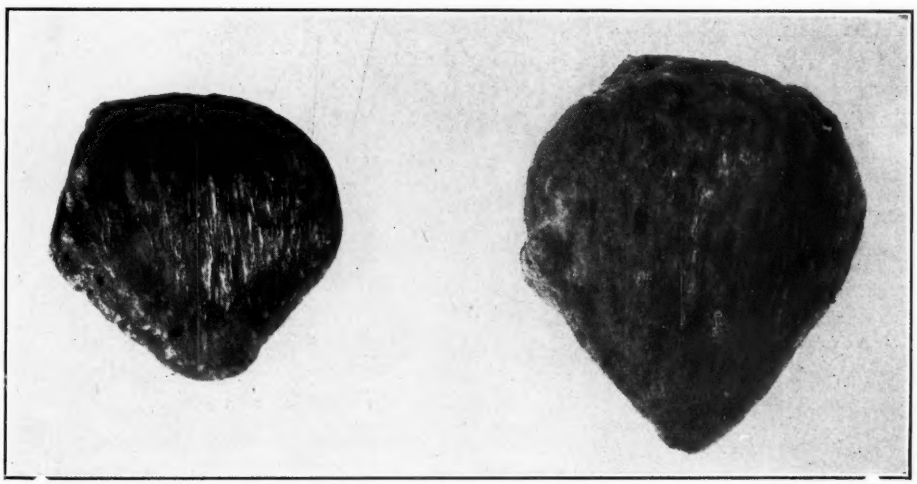

Fig. 14.—A normal patella (left) with patella from Case 2 on the right.

The patient was seen at frequent intervals and his only complaint was that of occasional frontal headaches which were controlled with aspirin. On every occasion when his urine was tested, it contained sugar, but this did not seem to upset the patient in any way.

Fig. 15.

Fig. 16.

Fig. 15.—Photograph of L. W. (Case 2) at the age of one year.
Fig. 16.—Photograph of L. W. (Case 2) at the age of fourteen years.

Fig. 17.

Fig. 17.—Photograph of L. W. (Case 2) at the age of seventeen years.

He was admitted to hospital in 1933, at the age of thirty-eight years, when he was a typical acromegalic with a very pronounced lower jaw, an enlarged skull, and a pituitary fossa six times its normal size (Fig. 6). His urine still contained some sugar but no other abnormality. He was passing, on an average, sixty-six ounces of urine per diem. There was a slight peripheral constriction of the visual fields. His vision was excellent and there was no sign of papilledema. The patient

Fig. 18.—Photograph of L. W. (Case 2) at the age of thirty-eight years.

Fig. 19.—Side face photograph of L. W. (Case 2) at the age of thirty-eight years, showing pronounced lower jaw and kyphosis.

had a marked cervicodorsal kyphosis of the spine but walked quite well. The headaches became less numerous, but he was inclined to get tired on slight exertion and was listless at times. He went to Brighton to stay with his brother and was able to get about until August, 1934, when he contracted what was thought to be heat stroke and died within twelve hours. His age was then thirty-nine years.

The patient had left his body for dissection purposes, and an extensive postmortem examination was made. The brain weighed seventy-four ounces, the pituitary body was enormous (Fig. 7), and the optic nerves were flattened out over the tumor, while the internal carotid arteries were displaced laterally. The microscopic appearance of the pituitary was that of a typical chromophile adenoma (Fig. 8). The skull was considerably enlarged in all directions (Figs. 9 and 10), and the lower jaw allowed a normal mandible to be placed inside it (Fig. 11). The vertebral column showed evidence of considerable growth and enlargement (Fig. 12). The increase in size of the long bones was very marked (Fig. 13), and definite signs of osteoarthritis were present at the knee and hip joints. The patella was about double the size of a normal bone (Fig. 14). In studying the photographs of this case, there can be no doubt that the condition of acromegaly commenced about the age of seventeen years and gradually progressed until the patient's death at the age of thirty-nine years. (See Figs. 15, 16, 17, 18 and 19.)

*Remarks.*—Up to the end of the year 1936 there are 299 reports of the autopsy findings published in the literature, and the condition of the pituitary gland has been described in 279 of these. Adenoma has been reported in 121 cases, but there is little doubt that in many of the other cases published before the histology of the pituitary gland was thoroughly understood the classification of the tumors said to be found was not correct; this especially refers to the cases of malignancy, but at the same time we are of the opinion that malignant disease of the hypophysis is more common than is generally believed. The finding in the case just described agrees with the now commonly expressed view that a chromophile adenoma, giving rise to hyperpituitarism, is the cause of acromegaly. The three chief interesting points in this second case are the huge pituitary fossa, the very large hypophyseal tumor, and the excessive weight of the brain. It is remarkable that the size of the tumor did not produce any greater disturbance of the eyesight than a slight peripheral constriction of the peripheral field. This is probably due to the enlargement of the pituitary fossa progressing *pari passu* with the increase in size of the hypophysis, so that little or no pressure was exercised on the optic nerves. We are not aware that so great an increase in weight of the brain has been reported previously. In acromegaly the greatest weights with which we are acquainted are those mentioned by Holsti (sixty-six ounces), and Fritsche-Klebs (sixty-three ounces). This case belongs to the chronic type, which includes the majority of cases.

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# OSTEOMYELITIS OF THE SCAPULA

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THIS communication concerns itself with osteomyelitis of the scapula. It will limit itself to those cases induced by the ordinary pyogenic organisms, staphylococci, streptococci, etc., and will not consider any case due to infection by the tubercle bacillus, the *Spirochaeta pallida*, or other extraordinary infecting organism, or any case of infection occurring in a neoplastic formation. A fair-sized literature exists concerning osteomyelitis of the scapula, consisting of isolated case reports for the most part and of one or two papers which attempt any discussion worthy of the name. It is noteworthy that, except for several isolated reports in the English language, all of the communications are found in the European literature, for the most part from the French and Italian sources. The best available report is that of Guibal and Montagne.[16]

## ANATOMY

Structurally the scapula is a combination of a flat and an irregular bone. The expanded portion of the scapula plate resembles the plate structure of a skull bone in that it consists of two opposed layers of periosteal bone; nevertheless, no intervening tissue resembling the cranial diploe is present. In the expanded portions of the glenoid process, the acromion and the coracoid, the structure is that of any irregular bone, i.e., a thin cortex of compact bone containing within its interior a mass of cancellous bone. The central part of the supraspinatous and the infraspinatous part of the bone are usually semitransparent; here the bone is occasionally deficient, and the opposed muscles are separated by fibrous tissue.

The scapula is ossified from seven or more centers: one for the body, two for the coracoid process, two for the acromion, one for the vertebral border, and one for the inferior angle. At birth, a large part of the scapula is osseous, but the glenoid cavity, the coracoid process, the acromion, the vertebral border, and the inferior angle are cartilaginous. During the first year, ossification begins in the coracoid process. Between the fourteenth and twentieth years, ossification of the remaining parts takes place, but the various epiphyseal lines still remain. The epiphyses are solidly united, the one to the other, by the twenty-fifth year. Failure of bony union between the acromion and the spine sometimes occurs, the junction being effected by fibrous tissue or by an imperfect articulation. The differentiation between an ununited epiphysis and a fracture can be readily made by comparing the two sides: ununited epiphysis is bilateral; whereas, ununited fracture of the acromion is almost invariably unilateral.

Received for publication, July 28, 1937.



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The bone is well covered with periosteum, except over the coracoid and the joint margins of the glenoid process; here, as well as over the borders of the spine and the margins of the scapular plate, the periosteum fuses with muscular and ligamentous attachments and loses its strict identity.

BLOOD SUPPLY

The blood supply of the scapula is a very abundant one. The chief sources of supply are delivered through the following large arterial trunks:

The subscapular artery, the largest branch of the axillary, arises opposite the axillary border of the subscapular muscle and runs down-

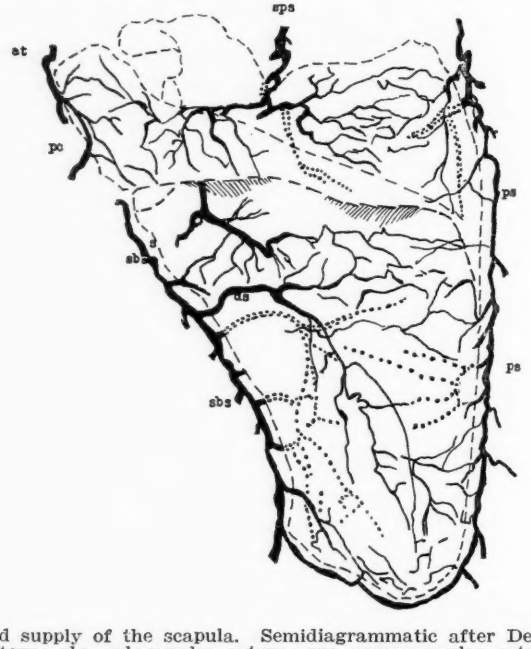


Fig. 1.—Blood supply of the scapula. Semidiagrammatic after Deaver: *ps,* posterior scapular artery; *sbs,* subscapular artery; *sps,* suprascapular artery; *ds,* dorsalis scapula artery; *at,* branch of acromiothoracic artery; *pc,* branch of posterior circumflex artery.

ward along the outer border of the scapula to its inferior angle where it anastomoses with the posterior scapular artery and with the long thoracic and the intercostal arteries. Four centimeters from its origin, it gives off a long branch, the dorsalis scapulae (circumflex scapular) artery, which winds around the axillary border of the scapula between the subscapularis and teres minor to the dorsum of this bone, where it anastomoses with the suprascapular and posterior scapular arteries. A small branch is given off from the dorsalis scapulae which enter the subscapular fossa beneath the subscapular muscle. A line drawn along the axillary border of the scapula to its inferior angle indicates the course of the subscapular artery.

The posterior scapular, the descending branch of the transverse cervical artery, passes downward under the vertebral border of the scapula, between the levator anguli scapulae and the rhomboidei muscles behind and the serratus magnus muscle in front, to the inferior angle of the scapula, where it anastomoses with the terminal portion of the subscapular artery. In its course it gives off numerous branches, which ramify on the posterior and anterior aspects of the scapula. The branches of this artery anastomose with the suprascapular, dorsalis scapulae, subscapular, and branches of the intercostal arteries. The posterior scapular often arises from the third portion of the subclavian artery.

The suprascapular artery, a branch of the thyroid axis, after passing along the under surface of the posterior belly of the omohyoid muscle, enters the supraspinous fossa beneath the supraspinatus muscle and passes around the lateral border of the spine of the scapula and enters the infraspinous fossa. Within these two fossae it supplies the supraspinatus and infraspinatus muscles, and anastomoses with the posterior scapular and dorsalis scapulae arteries.

The acromiothoracic branch of the axillary artery sends a tributary which ramifies around the acromion process. A branch of the posterior circumflex artery also ramifies around the lower aspect of the acromion process and anastomoses with the preceding.

## STATISTICS

During the period of twenty-five years from 1898 to 1923, 942 cases of hematogenous osteomyelitis were treated at the University Hospital of Helsingfors.[18] In 4 (0.42 per cent) the condition was localized in the scapula. In a review of the literature in 1911, Strauss found only 31 such cases. The number collected by Heinonen[18] up to 1925 is 46. Gaugolphe* in his series of 161 cases of osteomyelitis found only 9 cases with such a localization. Hooga in 414 cases of skeletal infection saw the scapula affected only 8 times. Fronber† had 24 scapula cases in 104 cases of osteomyelitis of all kinds. In Trendel's[47] series of 1,058 cases of osteomyelitis, 5 cases occurred in the scapula. In the cases admitted to Mount Sinai Hospital between the years 1923 and 1931, there was 1 case of osteomyelitis of the scapula in a total of 565 cases.

In the larger series of cases of osteomyelitis in general (Hilpert, Speed, Farr, Klein, Gibson, Huebler, etc.), to which I have referred on many previous occasions, there is apparently no experience with osteomyelitis of the scapula.

*Gaugolphe is quoted by Cinquemani.[8]
†Fronber is quoted by Cinquemani.[8]

### CLASSIFICATION OF CASES OF OSTEOMYELITIS OF THE SCAPULA

There is no reported experience of the extension form of osteomyelitis of the scapula. Only primary cases and cases of hematogenous infection are on record.

### PRIMARY OSTEOMYELITIS OF THE SCAPULA

Primary osteomyelitis of the scapula, as its name implies, occurs only after the production of open wounds extending down to or through the scapula. These are limited, practically speaking, to wounds produced by the various forms of firearms. War wounds, as Penhallow describes, present lesions similar to those in other bony structures and consist of perforations or grooves from bullets, various forms of comminution produced by bullets and other projectiles, and smaller and larger loss of bone tissue in the large ragged wounds produced most commonly by shell fragments. Any portion of the scapula may be involved in such wounds. There need not necessarily be any wound of the chest wall or any intrathoracic disturbance, although only too often these coexist with the larger type of wound, and under such circumstances a fatality is the rule, and that, too, quickly; infection of the bone has no time to develop. Infection commonly develops in the other types of wounds; the necessary debridement may be difficult to carry out; sinuses develop and persist after repeated revisions; and healing occurs only after extensive resections of bone which tax one's ingenuity in order to avoid extraordinary loss of tissue and undue disturbance or limitation of function and mobility.

Penhallow's case was that of a young soldier with a bullet wound which traversed the neck of the scapula. A persistent sinus developed. There was marked atrophy of the deltoid and biceps as well as loss of motion in abduction. There were numerous revisions, and healing occurred only after the entire sinus tract was dissected out.

### HEMATOGENOUS OSTEOMYELITIS OF THE SCAPULA

Except for some factors peculiar to its anatomic structure and to its location, hematogenous acute osteomyelitis of the scapula differs in no way from similar forms of osteomyelitis in any of the other flat and irregular bones of the skeleton. All of the facts applying to the etiology, bacteriology, mechanism of infection, pathology, and pathogenesis which I have described and discussed on many previous occasions, and which I have also included in my book, apply to hematogenous acute osteomyelitis of the scapula.

*Pathogenesis and Pathology.*—The pathology, pathogenesis, and mechanism of hematogenous acute osteomyelitis in the scapula is exactly similar to that in the other bones of the body and is based upon the formation of a thromboembolic lesion in the vascular plexus of the bone. Because of the essential anatomic and vascular conditions, there is no

repetition of the typical distributions seen in the long bones; and the lesions produced in the scapula are of irregular size and shape and are determined by the anatomic arrangement of the blood vessels. In the scapula the lesions vary from inconsequential segments to involvement of nearly the entire anatomic segment. In the thin expansions of the supraspinatous and infraspinatus fossae, the complete development of the osteomyelitis is frequently followed by oval or circular deficiencies in the bone structure. Periosteal lesions are just as common as lesions involving the entire thickness of the bone. In the thin plate of the scapula, defects of bone tissue produced by exfoliation of necrosed bone are most commonly not made good by osseous tissue; a thin fibrous tissue membrane, really a thin expanded scar, comes to occupy the place of the cast-off bone.

*General Symptomatology.*—The general symptoms and course of an acute hematogenous osteomyelitis of the scapula differ in no way from that present when the disease attacks other bones of the skeleton. This is especially exemplified when multiple lesions are present and one of these is located in the scapula. The several groupings into fulminant hyperacute and moderately severe infections are present in these cases also.

In the hyperacute cases, the clinical picture is that of a profound and overpowering general infection and intoxication of the entire system. There are initial chills and subsequent high fever and the general condition rapidly becomes very bad. Blood cultures are positive as a rule. The signs of any local disease are at a minimum, are frequently wanting, and, when present and looked for, are not easily demonstrable owing to the tremendous intoxication which is present. In the most severe cases death follows in a few hours from the general infection. From the group of terribly severe and dramatic cases all grades of intensity of infection exist down to those described in the following sections.

In the moderately severe, or ordinary type of case, the onset is characterized by general symptoms, such as chills, fever, vomiting, nervous irritability, rapid pulse, scanty urine, and grave general condition. In many cases there is nothing to call attention to the region of the shoulder during the first hours. However, more frequently the general symptoms are accompanied by local symptoms. The shoulder is swollen and painful, the skin is smooth and hot and the veins are dilated. The pain may prevent spontaneous movements. At any moment the symptomatology may become most grave; the general blood infection increases to such an extent, that the patient may die either with or without well-developed local signs of the infection.

In the very severe cases the diagnosis is frequently in doubt beyond the bare fact of a general infection being present. Erroneous diagnoses are common: frequently typhoid fever is assumed to be the dis-

ease; or because the character of the symptomatology is markedly influenced by the rapid development of some complication within the meninges, it is thought that a cerebrospinal meningitis is present: examples of this kind are numerous in the literature.

The differential diagnosis is not only difficult as between the presence or absence of an osteomyelitis, or between the latter and some other condition in the very severe and grave cases referred to; but even in cases of lesser magnitude of intensity, it may also be extremely difficult to accurately localize the focus of infection in the glenoid, coracoid, or acromion processes as opposed to a localization in the shoulder joint or in the head or neck of the humerus, even when the local signs and symptoms of pain and tenderness, general tumescence, and limitation of motion are present and are marked. Roentgenographic studies do not give any indication of the localization in the first ten days of its development and are, therefore, of no help then. Later, however, the differentiation and localization are easily made by roentgenographic means.

*Local Symptomatology.*—The most typical symptoms are due to local suppuration and to the extension of the suppuration to the soft parts. The localization of the suppuration is determined by the area of bone involved and its anatomic position must necessarily conform to the gross architecture of the bone and to which aspect—ventral or dorsal—of the bone houses the thromboembolic lesion. Various symptom complexes are therefore distinguishable which conform to these criteria; they are as follows:

1. Supraspinatous fossa cases.
2. Infraspinatous fossa cases.
3. Spine cases.
4. Acromion cases.
5. Coracoid cases.
6. Subscapular fossa cases.
7. Cases with shoulder joint involvement.
8. Axillary space cases.
9. Diffuse or total scapula cases.

1. *Supraspinatous Fossa Cases.*—The signs are those of an inflammation of the neck or supraclavicular region. The supraspinous region is swollen, shiny, and red. There may be a torticollis from contracture of the trapezoid muscle. Palpation shows the extent of the swelling and the point of maximum osseous pain. Fluctuation occurs late. Depending on the location of the involved part of the bone, the maximum osseous pain may be found on the coracoid process, along the posterior edge of the spine and the acromion, at the superior and internal angle or in the supraspinous fossa. The muscles show a reflex contracture and their reaction is manifested by a limitation in the movements of the arm. Extension of the initial suppuration may occur toward the

posterior region of the neck under the trapezius, toward the clavicular region, toward the subspinous fossa, toward the subscapular fossa, or toward the axilla.

The underlying bone involvement may be present in the part of the scapula plate above the spine, in the upper aspect of the spine, in the acromion, or in the coracoid, or in more than one of these.

2. *Infraspinatous Fossa Cases.*—The signs are those of diffuse suppuration of the scapula or dorsal region. The inflammatory swelling predominates below the spine of the scapula and extends toward the inferior angle. The swelling is less tense than in the supraspinous region as there is a greater cavity in which the pus may accumulate. The maximum osseous pain is along the internal margin of the scapula, at the inferior angle, or along the lower edge of the spine. The muscles involved in the process are the subspinous, deltoid, and rhomboid. Painful retraction of these muscles is manifested by limitation of rotation of the arm, adduction of the arm and displacement of the scapula outward. Extension of the suppuration may occur along the deltoid, to the subscapular fossa, toward the axilla, or to the dorsal or dorsolumbar region. The prognosis of this form is somewhat more grave than that of the preceding on account of the greater frequency of a total suppuration of the bone and the extent of the necessary resection.

The underlying bone involvement is present in the expanded portion of the scapula below the spine and on its dorsal surface, or in the lower aspect of the spine.

3. *Spine Cases.*—The symptoms imitate those of the cases in Groups 1 and 2 in accordance with the aspect of the spine which bears the brunt of the lesion. Both localizations may be involved. Parts of the spine become detached as necrosis and exfoliation occur. Extension of the suppuration is not as marked and localization is easily made out and occurs early. The prognosis is relatively good in these cases.

4. *Acromion Cases.*—These are the simplest of the cases; they are easily and quickly localized and detected. The disability is quite marked, especially as regards elevation of the arm. The acromioclavicular joint is commonly involved. Suppuration occurs frequently in the subdeltoid bursa. There are some similarities to the spine cases in Group 3. During the exfoliation of any necrosed bone, the acromion may become detached, increasing thereby the functional disability.

5. *Coracoid Cases.*—The symptomatology is rooted at the base of the neck and within the superior aperture and the extreme upper part of the thoracic cage. Suppuration occurs within this environment. Most commonly, however, the abscess tends to localize beneath the deep pectoral muscle (subpectoral abscess), and from there it tends to spread into the axilla. The only muscle directly involved is the pectoralis minor muscle; the importance of this muscle is minimal, but,

nevertheless, evidence of its disability is found in the pain and limitation of motion of the thorax on the involved side. Thrombosis of the axillary vessels may be a complication, and neuritic pains referred to the cords of the brachial plexus may be a source of great discomfort.

6. *Subscapular Fossa Cases.*—The clinical aspect is that of a deep-seated suppuration. There is an abnormal elevation over the entire scapula. The patient complains of a dull, deep thoracic pain before the appearance of these symptoms and while there is no appreciable modification of the scapular region. Palpation may give the impression that the scapula rests on an elastic foundation. The only muscle directly concerned is the subscapular. Painful retraction of this muscle is manifested by limitation in external rotation and in elevation of the arm. Local extension may occur mesially toward the internal edge of the bone, and outwards towards and into the axilla. Cases are also described where the suppurating process has perforated the chest wall and caused an empyema. In addition, if, because of necrosis and exfoliation, perforation of the scapular plate should occur, the suppuration extends anteriorly and spreads beneath the infraspinatous muscle. I have not been able to find any cases where this phenomenon occurred through and into the supraspinatous fossa. Thrombosis of the axillary vein may occur. Because of all of these complications, the extent of bone involvement and of the suppuration, and the magnitude and seriousness of any operation, the prognosis of this form is bad.

7. *Cases With Shoulder Joint Involvement.*—The signs are those of an acute suppurative arthritis of the shoulder joint. There is considerable swelling of the soft parts and the entire upper extremity is immobilized and fixed by contractures of the muscles. Extra-articular abscess formation only occurs after perforation of the capsule when the usual signs of a superficial or deep-seated abscess in the soft parts become elicitable. Local extension of the extra-articular abscess occurs to the axilla, subpectoral space, or subscapular fossa. Other parts of the scapula may be involved and also the head of the humerus. An alarming general blood infection is more frequent in this form than in the others and hence the prognosis is very grave.

8. *Axillary Space Cases.*—Symptoms referred to the axillary space, as can be seen from this classification, occur with the cases in a number of the previously described groups, most commonly when the bone focus borders the axillary space. Quite commonly the axillary suppuration is part-and-parcel of a subpectoral abscess. The clinical aspect is that of abscess of the axilla. The axilla appears to be swollen and the arm is in abduction. Palpation shows a more or less painful and hot mass. The swelling is independent of the articulation. There may be a painful osseous point on the coracoid process or at

the anterior part of the neck of the scapula. The muscles involved are those which limit the axillary cavity. Their reaction is manifested by a limitation of elevation of the shoulder, adduction of the arm and external rotation. The impotence may be complete. Extension may occur toward the shoulder joint, toward the thoracic wall, or to the vascular sheath of the axillary vessels.

9. *Diffuse or Total Scapula Cases.*—The symptomatology of the cases in this group combine all of those described in the previous classifications. There are present diffuse local signs which give the impression of a diffuse abscess of the shoulder region. The swelling extends around the shoulder and over the entire scapular region. The entire scapula is tender. Movements of the scapula on the thorax are suppressed while those of the humerus are rendered impossible by the pain even if the articulation is intact. This form is particularly serious because of the frequency of a severe general blood infection.

My case was that of a young child with the signs of a very severe general blood infection and local symptoms referable to the shoulder and the entire scapula. At operation suppuration was demonstrated in the infraspinatous fossa and through a trephine opening in the subscapular fossa. The child died several hours later. Involvement of almost the entire scapula was found at the postmortem examination.

## ROENTGENOLOGY

In clinical practice the differentiations outlined in the previous classifications are not entirely or clearly manifested in the physical examination of the patient. Overlapping of clinical pictures is common. Knowledge of the actual part of the bone involved and its extent depends almost entirely upon roentgenographic observation and study.

In general with all roentgenologic facts relating to bone tissue, it must be remembered that bone lesions take a relatively long time to develop sufficiently to give differentiating shadows on the x-ray plates. Where the periosteal layers are fully developed and can be clearly visualized in the pictures, the first signs of change are linear differentiations of the periosteum which grow thicker as involucrum is deposited. It is easier to see these changes in lateral pictures, which show the scapula "on edge." As a general rule, it takes eight to ten days before these changes can be first perceived. The next changes occur in the bone tissue and vary, in accordance with the length of time interposed from the beginning of the pathologic process, from smaller and larger areas of rarefaction to areas of necrosis and to completely differentiated and separated sequestra of various sizes and shapes. In the thin plates of the scapula, perforations are common. In the late stages the effects of destruction of bone tissue are easily visible, both in the amount of tissue destroyed and in the compensat-

ing changes of morphology of the remaining portions, as well as in the amount of involucrum which is formed. Comparison of the two sides commonly gives striking effects.

Roentgenographically visible sequestration and exfoliation of bone are most commonly seen in the acromion, the spine, and the lower angle of the scapula in relatively large masses of dead bone.

### COMPLICATIONS AND SEQUELAE OF ACUTE HEMATOGENOUS OSTEOMYELITIS OF THE SCAPULA

The complications of acute hematogenous osteomyelitis of the scapula, in common with other forms of similar lesions in other bones, are of two varieties: (1) those due to the general infection (bacteriemia) to which the scapular lesion is secondary; and (2) those due to the local process itself. The first of these has been discussed on many previous occasions and the interested person is referred to previous publications and to my book on osteomyelitis for exhaustive studies of this aspect of the subject. The local complications of the scapular lesion are as follows:

1. The local forms of suppuration have already been discussed.
2. Thrombosis of the adjacent axillary vessels.
3. Neuritic manifestations referred to the bronchial plexus.
4. Various forms of arthritis and suppuration in the shoulder joint.
5. Various degrees of ankylosis in the shoulder joint.
6. Empyema thoracis and mediastinitis due to chest perforation of a subscapular abscess.
7. Fixation of the scapula by adhesions, etc.

### TREATMENT

In the primary cases of acute osteomyelitis of the scapula, the treatment is entirely prophylactic in the beginning and aims to prevent the appearance of any osteomyelitis by proper debridement and antisepsis of the wound. In the late stages, when the prophylactic treatment proves inefficient, the same principles of treatment prevail as for any other form of osteomyelitis of the scapula.

The general principles of treatment of the hematogenous form of osteomyelitis of the scapula are no different than when the infection centers in any other bone of the body and the reader is referred to the chapters in my book which deal with this aspect of the subject exhaustively. Suffice to reiterate here only those important points upon which the modern treatment of hematogenous osteomyelitis is built:

1. The importance of recognizing the fact that in the early stages the treatment is based upon the presence or absence of the accompanying general infection, and upon its intensity or progression; and

it should be recognized that the outcome, as far as life is concerned, depends upon the general infection and not upon the local lesion.

2. The importance of assuming a most conservative attitude so that nature can properly localize the lesion and limit the suppuration, necrosis, and sequestration, and so that the least possible intervention of surgery can be practiced.

3. The value of rest and immobilization of the arm during the early stages and, in fact, during all stages of the illness.

4. The necessity, because of this attitude, of limiting one's operation in the beginning to the incision and drainage of frank abscesses and of not interfering with the bone structure.

5. The importance of waiting until sequestration is complete before attempting to remove the diseased part of the bone.

6. When the time for sequestrotomy arrives, the importance of planning the operation so that the minimal amount of damage is done to neighboring and adjacent structures—bone or soft tissue.

7. The necessity and importance of keeping up the general nutrition and condition of the patient on as high a plane as possible by all supportive measures during the entire course of the illness and as preliminary preparation before any operation; this includes the use of blood transfusions.

In accordance with these criteria the treatment of acute hematogenous osteomyelitis of the scapula narrows itself down to (1) incision and drainage of abscesses; and (2) the secondary sequestrotomy which is almost always necessary. The discussion of the problem concerns itself mostly with the consideration of the best methods of approach and the lines of incision for the proper performance of these operations.

For all methods of approach, the best position of the patient is prone upon the abdomen and the best position of the arm is abduction at ninety degrees. The general lines of incision run along the edge of the spine of the scapula and at the inner or outer edge of the body of the scapula; in suitable cases the two lines may be combined in a T-shaped incision. For each individual case, the operator must use his own judgment as to the position, length, etc., of the incision or incisions. Approach to the abscesses should be made between the periosteum and the bone, and free drainage should be provided. In the subscapular cases it is frequently necessary to trephine the bone in order to obtain adequate drainage.

In doing the secondary sequestrotomy, or in late operations for unhealable sinuses or recrudescences, similar criteria as to the position of the patient, etc., prevail. The important point always to remember is to eliminate all obstacles to the healing of the wounds, as I have previously described in my book; and to do all necessary manipulations subperiosteally in order to encourage re-formation of the scapula to as large an extent as possible.

The best position for shoulder joint cases is on the side. The general principles for the drainage of the joint should be followed. The patient should be placed either on his abdomen or back according to the incision adopted. A posterior incision is to be preferred. The deltoid should be retracted outward and it may be necessary to section the acromion obliquely from the middle of the spine to the external edge. If the inflammatory symptoms predominate anteriorly, an anterior incision can be made descending from the clavicle in the deltopectoral groove. The articular capsule should be widely opened and the foci should be curetted. It may be necessary to resect the glenoid cavity and sometimes the head of the humerus. The late functional results of this operation are generally satisfactory and sometimes even surprising if the humerus is suspended from the clavicle or acromion.

Where the bulk of the objective manifestations lie anteriorly, or in the axilla, the patient should be placed on his back with his arm in slight abduction. An interdeltopectoral incision is the best. Resection of the coracoid process may be necessary. All lesions on the external edge or anterior surface of the neck should be curetted, care being taken not to open the articulation. Drainage of the axilla can be assured by a long incision at the inferior edge of the great pectoral muscle.

In extensive and very bad cases it may be necessary to remove the entire bone, but the articular portion should naturally be respected if there is no suppurative arthritis. The acromion and coracoid should be spared if possible. The patient should be placed on his abdomen with his shoulder elevated by a cushion. Two forms of incision are possible, a double vertical incision along the internal and external edges or an internal vertical incision combined with a horizontal incision extending along the posterior edge of the spine. The latter incision is best. The periosteum should be incised and separated on the spine of the acromion, the angles, and the spinous fossae. All of the muscular attachments are separated. After the scapula has been liberated in this manner, it is turned outward and posteriorly so that the clavicular attachments can be sectioned. The neck should be sectioned with a Gigli saw. The results are satisfactory in many cases and a useful arm may be retained.

In all of the chronic cases, cicatrization and healing are aided and hastened by generous supportive measures; and nowhere are they more important than with these extensive cases. In the literature there are some good reports regarding the efficacy of ultraviolet radiation.

The functional results depend to a large extent upon the amount of re-formation of the architecture of the scapula, upon the amount of destruction or scarring in or about the muscles, and upon the amount of disturbance in the shoulder joint. As a general rule, where the latter factor is not present, the functional results are very fair. There

is a marked tendency for recrudescence, or inability of the wounds to heal, and many revisions may be necessary. Total scapulectomy is sometimes done as a last resort.

The mortality is similar to that of osteomyelitis in other bones; and in extensive operations the latter themselves carry an additional risk.

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# GRANULOMA VENEREUM (GRANULOMA INGUINALE) OF UTERUS, TUBES, AND OVARIES

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THE specific histology of granuloma inguinale was recently described by Pund and Greenblatt,[1] and they emphasized the comparative ease of diagnosis. The tissues were fixed in neutral 10 per cent formaldehyde solution, embedded in paraffin, sectioned, and stained by Delafield's hematoxylin method and with eosin. In the sections there were encountered, in variable numbers, large cells of a peculiar type that contained many intracytoplasmic spaces, which in turn contained small, purplish-stained bodies. This cell was denoted as the pathognomonic cell. It is a large mononuclear cell that varies from 25 to 90 microns in diameter. One or many intracytoplasmic cysts may occur in a cell. The bodies within these cysts are grouped peripherally. In a subsequent article[2] they observed that the specific cell, laden with the Donovan bodies, was more readily demonstrated with the use of the silver impregnation method of Dieterle[3] (see Fig. 1). The cell outline, nucleus, and cyst walls stain pale yellow, while the Donovan bodies appear as dark brown or black rectangular or elongated ovoid forms with intense bipolar staining. These bodies, because of their contour and polar characteristics, resemble a safety pin.

In this second publication[2] they described a previously suspected but not established entity, namely, involvement of the cervix of the uterus by this specific granulomatous infection. At this time they used the obviously preferred term granuloma venereum in place of granuloma inguinale. We shall therefore use the suggested term here. Based upon the criteria established by these observers, we are reporting what we believe the first recognized case of granuloma venereum of the body of the uterus, the tubes, and the ovaries.

## CASE REPORT

A negress, aged twenty-eight years, para two, entered the University Hospital because of pain and a palpable mass in the left lower abdominal quadrant, uterine hemorrhage, fatigability, and loss of weight. The slowly enlarging mass had been noticeable for five months and for the past two months had been associated with localized intermittent lancinating pain. Uterine bleeding had been excessive for the past two months and was worse following coitus. Her menses had been irregular and leucorrhea had been noted since the birth of her second child eight months ago. Examination revealed an enlarged firm, red cervix which bled easily on touch. The

Received for publication, July 12, 1937.

pelvis was filled by a large hard fixed mass that extended almost to the umbilicus A catheterized specimen of urine from each ureter contained a number of pus cells, and colon bacilli were obtained on culture. An active minimal pulmonary tuberculosis was found on physical and x-ray examination, and on one occasion acid fast organisms were observed in the sputum. Secondary anemia was evident by an erythrocyte count of 2,000,000 cells per cu. mm. and a hemoglobin estimate of 36 per cent. White blood cells were 15,000 per cu. mm. with 85 per cent polymorphonuclear leucocytes. The Wassermann and Kahn reactions on the blood were negative. There was remittent fever between 100° and 104° F. Tentative diagnoses were chronic inflammation of the cervix, fibromyomas of the uterus, and chronic pelvic inflammatory disease; pyelitis secondary to an obstructive pelvic mass; minimal active pulmonary tuberculosis.

Under conservative treatment for two months there was no improvement, so operative interference was deemed advisable. The uterus, tubes, and ovaries were

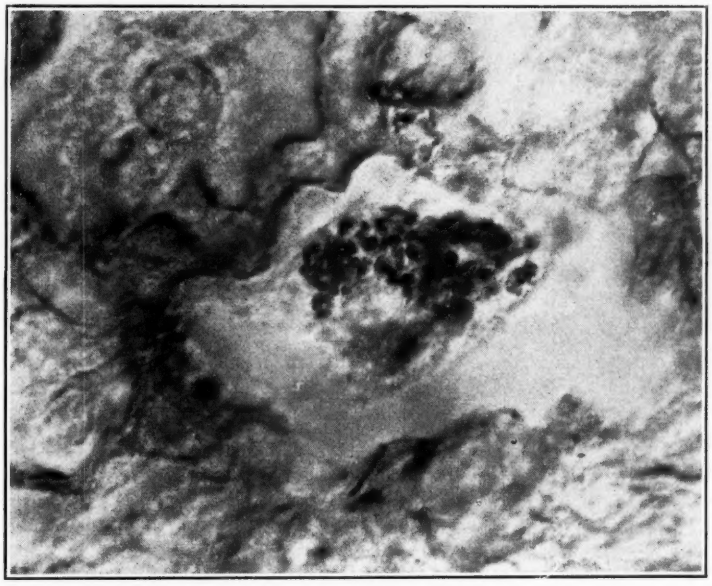

Fig. 1.—A pathognomonic cell in a section from the myometrium stained by Dieterle's silver technique. The spherical grouping of the Donovan bodies is due to their intracystic position. The peripheral distribution of the bodies in the cysts is indicated by the group in the upper right corner, the center of the cyst being in focus. Note the safety-pin appearance of some of the intracystic bodies (×3,500).

removed with difficulty because of dense adhesions binding them to the pelvic colon and loops of small intestine. The pelvic peritoneum was studded with minute grayish yellow foci. The uterus was so friable that in removing it the body was torn from the cervix and very little bleeding occurred. The postoperative impression was tuberculosis of tubes, ovaries, uterus, and pelvic peritoneum. Death occurred from shock the day following operation. Permission for necropsy was refused.

## PATHOLOGIC DESCRIPTION

The tubes, ovaries, and uterus were bound together by dense fibrous adhesions. Only the body of the uterus was received and measured 10 cm. long, 9 cm. broad, and 5 cm. thick. The cervical end was

ragged and friable. The endometrial surface was yellowish gray, granular, and not clearly defined from the myometrium. The myometrium appeared fibrous and was studded with minute gray and light yellow foci. The tubes were tortuous and moderately thickened and the lumina were obliterated in the uterine two-thirds. The fimbriated ends were sealed. Where the lumen was patent, the mucosa appeared gray and granular. Yellow foci were noted in the walls of the tubes. The ovaries were spherical, firm, and enlarged to 5 and 7 cm. in diameter respectively (Fig. 2). The cut surface of both was fibrous and numerous soft minute yellow foci were scattered throughout.

Fig. 2.—Left ovary, longitudinal section. Note the symmetrical enlargement and solidarity.

MICROSCOPIC EXAMINATION

In sections from the uterus, the endometrium was disorganized so that only an occasional tubular gland was encountered. Beneath a superficial necrotic zone, there was a dense exudate of polymorphonuclear leucocytes, lipoid-laden histiocytes, and much fibrin. Hemorrhage had occurred at sites of scant granulation tissue formation. The muscle bundles of the myometrium were dissociated by a heavy cellular exudate of plasma cells, polymorphonuclear neutrophiles, and some lymphocytes accompanied by fibroblastic proliferation and a new growth of blood vessels (Fig. 3). Occasionally, ill-defined foci of necrosis were observed, and some were largely occupied by lipoid laden histiocytes. Cellular

exudate and fibrin partially filled many of the dilated lymphatics. The large pathognomonic monocytes with encysted bipolar staining bodies were seen in the cellular areas of granulation in both the endometrium and myometrium. The cytoplasmic wall of many of these cells had broken and the distended intracytoplasmic cysts had ruptured and spilled their small bacillary-like bodies.

In the tubes the cellular exudate and fibroblastic activity were most pronounced along the mucosa, which had been destroyed with the exception of an occasional epithelial lined space (Fig. 4). The slender muscle bundles were widely separated by proliferating and partially collagenized fibrous tissue. The character of the cellular exudate was

Fig. 3.—Section from myometrium. The muscle bundles are dissociated by the infiltrate of polymorphonuclear leucocytes and plasma cells with fibroblastic proliferation; hematoxylin-eosin (×280).

the same as in the uterus. The serous coat was edematous. The pathognomonic cell was present in considerable numbers in the granulomatous areas.

The ovaries were diffusely involved by a similar inflammatory process. Here, however, fibroblastic proliferation was more pronounced (Fig. 5). Foci of necrosis, infiltrated by large numbers of lipoid-laden cells, were numerous. Again the pathognomonic cell was readily demonstrated. An occasional hyalinized scar was the only recognizable ovarian structure.

Repeated examinations of sections from all organs failed to reveal acid-fast organisms.

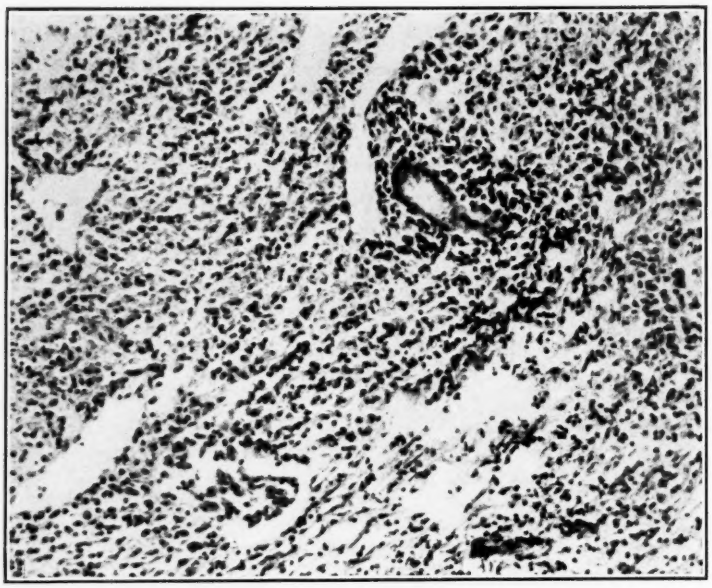

Fig. 4.—Section from tube. Destruction of the mucosa and obliteration of the lumen. A single tubular structure is all that remains of the mucous membrane in this section; hematoxylin-eosin (×280).

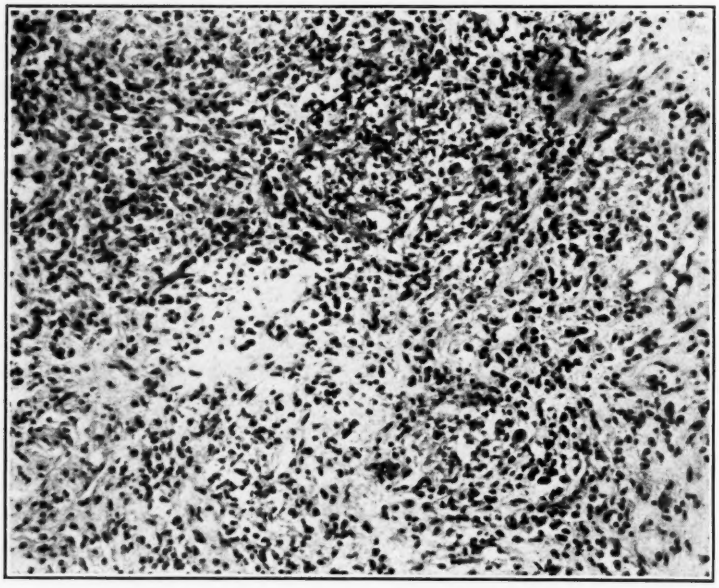

Fig. 5.—Section from ovary. Diffuse infiltration with plasma cells and polymorphonuclear leucocytes accompanied by fibroblastic proliferation; hematoxylin-eosin (×280).

## DISCUSSION

The histologic diagnosis of granuloma venereum is made by the demonstration of Donovan bodies in sections. The characteristic cell with the encysted bodies can be recognized in preparations stained with hematoxylin and eosin and also with silver salts. The bipolar effect and the safety-pin appearance of the bodies are better seen with the silver stain. The cyst wall and cell detail are more clearly demonstrated in hematoxylin-eosin preparations.

When the patient was first seen in the out-patient department of the hospital, the appearance of the cervix elicited a tentative diagnosis of carcinoma. At a subsequent, more thorough gynecologic examination during hospitalization, an inflammatory condition rather than carcinoma was suspected. In view of the universal involvement of the uterus, tubes, and ovaries in this case, we believe that the cervix was also involved and that here the primary lesion of granuloma venereum occurred. This probability is enhanced by its similarity to the lesions in the cases which were reported by Pund and Greenblatt.[2] The necessity of biopsy and histologic examination is obvious in the differential diagnosis of the affections common to the cervix. Furthermore, it has now been demonstrated that all the female genitalia may be the site of granuloma venereum. The possible concurrence of this disease in the body of the uterus, tubes, and ovaries should therefore be suspected in cases of uterine bleeding and pelvic inflammatory disease in patients with granuloma venereum of the cervix. It is to be especially noted that the symptoms in this case date from the termination of a normal pregnancy eight months previously. It is possible that the infection spread from the cervix to the body of the uterus, tubes, and ovaries following delivery. If conclusions can be drawn from one case, it would seem that granuloma venereum of the cervix may prove a serious complication of pregnancy.

Finally, certain features about the gross pathology, as seen in the uterus, tubes, and ovaries, are to be noted. The symmetrical proportions of the uterus, the uniform thickening of its wall which was studded with minute foci of suppuration, and the replacement of the endometrium by a necrotic pseudomembrane bespeak a widespread dispersion of the infectious agent through all the tissues of the organ. Of similar inference is the diffuse involvement of the tubes and ovaries. The spherical solid ovaries of large size would ordinarily have suggested neoplasm. We believe our case to be unique in that such solidarity of structure and uniformity of involvement were produced in these organs by an infectious agent, and we advance the opinion that such findings should induce the surgeon and the pathologist to suspect granuloma venereum.

## CONCLUSIONS

1. A previously undescribed entity is reported, namely, involvement of the uterus, tubes, and ovaries by granuloma venereum.

2. The difficulties in the differential diagnosis of granuloma venereum from the varied affections common to the female internal genitalia are emphasized.

3. The involvement of the cervix by granuloma venereum is of especial significance in regard to pregnancy. Following delivery it is possible for the infection to spread from the cervix to the body of the uterus and adnexa.

4. Certain peculiarities of the gross appearance of the internal female genitalia affected by granuloma venereum are noted: symmetrical enlargement of the uterus, fibrosis of the tubes, and a solid enlargement of the ovaries.

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# LYMPHOPATHIA VENEREUM: TREATMENT WITH DILUTED FREI ANTIGEN INTRADERMALLY AND OBSERVATIONS ON DIAGNOSIS*

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DeWOLF[4] and Cole,[5] through their recent contributions, have been most successful in arousing the interest of the American medical profession in lymphogranuloma inguinale. Wolf and Sulzberger in 1932 suggested the name lymphopathia venereum[2] for the disease, indicating that it is of venereal origin and one which attacks the lymph channels and nodes. This is in our opinion a better term to apply to the disease as it eliminates confusion with an entirely different malady, namely, granuloma inguinale, and by its own terminology does not localize the disease to any certain area. It is now recognized as a definite clinical entity, which is not peculiar to the tropical climate, but may be found rather commonly at any clinic where one looks for this disease. At the Norfolk Marine Hospital, during the past eleven months, we have made Frei tests on 115 suspected or doubtful cases and diagnosed 48 cases as lymphopathia venereum.

Lymphopathia venereum is a definite venereal disease occurring among both white and colored races. In the analysis of cases in various clinics, the preponderance of cases occur among the colored race. Males are affected apparently more often than females in both races. The disproportion will be less significant if we realize that the subacute symptoms of the disease are much less readily elicited in the female than in the male. In our series of cases, 10 were white and 38 colored. Of these 38 colored, 5 cases were in the female. Bernstein states[7] that recently infections have been noted in children.

## ETIOLOGY

The present consensus of opinions is that the causative agent is a filtrable virus, which in nearly every case is transmitted during sexual contact. Experimental transmissions of the virus to monkeys, guinea pigs, or mice have been reported. Some of the infected monkeys have died with meningoencephalitis. The virus can be destroyed by heating at 60° C.; it will not resist glycerin or dilute formaldehyde solution.

Patients frequently claim injury as the cause of their bubo. In 3 cases in our series which were diagnosed as lymphopathia venereum, there was a definite, proved history of trauma. In 2 of these cases the initial lesion preceded trauma to the gland. It is reasonable to conclude that injury was a factor activating the infection in the gland inasmuch as the disease manifested itself in the inguinal node which

*Approved for publication by the Director of the National Institute of Health.
Received for publication, July 17, 1937.

was traumatized and did not appear in the gland on the opposite side. However, there is a possibility that the trauma occurred as a coincidence.

### COMMENTS ON SYMPTOMATOLOGY AND CLINICAL COURSE

The initial lesion is transitory, heals spontaneously; and more often than otherwise, the patient's first knowledge of his disease occurs at the time a bubo makes its appearance, or in the case of a female, rectal stricture and/or esthiomene.

The period elapsing from the time of exposure to the appearance of the primary lesion is possibly a few days to one week. After an incubation period of from ten days to three weeks—rarely six weeks

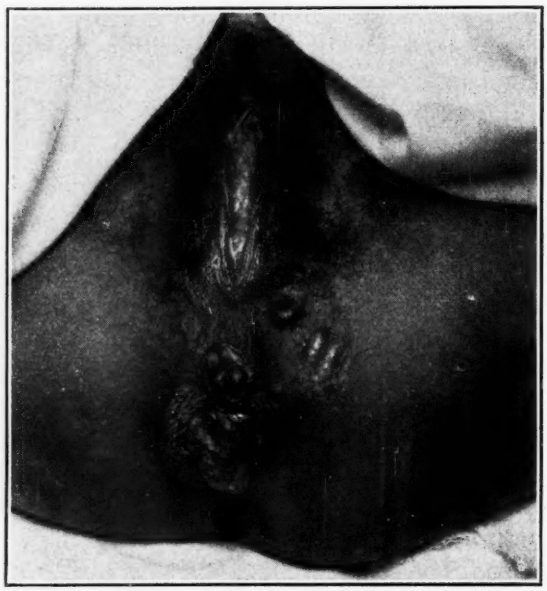

Fig. 1.—M. L. C., colored female, aged twenty-one years, entered the clinic Feb. 28, 1936, complaining of constipation, ribbonlike stools, rectal discharge with small amount of blood, and extreme pain on defecation. Symptoms have been of gradual onset over a period of approximately two years. In 1932 a hemorrhoidectomy was performed because of a mass protruding at the time of defecation (operation elsewhere). Examination reveals a pedunculated cauliflower-like growth almost encircling the anus, and slightly to the left and anteriorly are several sinuses, two healed and one still draining a thin grayish discharge. Rectal examination reveals an indurated constriction of the bowel which barely admits the tip of the index finger, 4 cm. proximal to anus. There also is exquisite tenderness. The Kahn reaction was four plus and the Wassermann strongly positive on two examinations. The Frei test was markedly positive. The patient did not return for treatment, but it was learned she is receiving antisyphilitic treatment elsewhere with symptomatic improvement, but the clinical findings as recorded remain the same.

postcoitus, the patient notes a swelling of the inguinal glands which may be mild or severe, unilateral or bilateral. Along with the formation of the bubo, generalized symptoms may make their appearance. The constitutional reaction consists of chilliness, lassitude, pains in the joints and muscles, headache, nausea, mild anemia, and loss of weight. There may be occasionally stiffness of the neck and other meningeal symptoms. Skin manifestations, such as erythema multi-

forme or erythema nodosum, may occur. The spleen may be enlarged. A temperature of 102° to 104° F. is not rare, and may persist for several weeks, continued quite likely by the involvement of new nodes.[4, 6, 9]

Quoting from DeWolf:[4] "The first glands to be involved are those of the superficial chain in the inguinal region. The disease progresses steadily, though usually slowly, to produce a mass which may reach the size of a fist—new glands becoming involved as the disease progresses, all being bound together by a periadenitis. This period of invasion may extend over several weeks before the disease reaches its

Fig. 2.—A. C., colored female, aged twenty-five years, entered out-patient clinic Sept. 1, 1936, complaining of swelling about vagina, vaginal discharge, and constipation accompanied by small ribbonlike stools, of approximately eight months' duration. Examination reveals marked spongy edema of right labia minora, to a lesser extent same condition of right labia majora, thin grayish vaginal discharge, pedunculated cauliflower-like growth attached to left side of anus, and marked constriction of rectum not admitting index finger, 2 cm. proximal to anus. Kahn four plus and Wassermann anticomplementary on two examinations. Frei test (four antigens) strongly positive. Readings made at forty-eight, seventy-two, and ninety-six hours with strong reaction each time. Last reading of each antigen 1.5 mm., 1.2 mm., 0.8 mm., and 1.1 mm. Because of marked reaction to Frei test, treatment was instituted with a 1 to 10 dilution of the original 1 to 24 dilution usually employed for therapeutic purposes. To date seven intradermal injections have been administered at five-day intervals without any improvement being noted.

maximum extent." The adenitis at its first stage presents a fairly uniform, indurated, and tender mass. As the bubo increases in size, it becomes adherent to the skin which is being put under a stretch, becomes shiny, and takes on a deep violaceous color. Soon the swell-

ing begins to fluctuate and characteristic fistulous openings, which drain a thin seropurulent fluid for weeks or months, make their appearance. Occasionally in the lymphopathia bubo there is never any suppuration or fistula formation. The disease usually runs a chronic course and the formation of a heavy scar tissue frequently marks the final outcome of the lesion.

In some of the cases the perirectal lymph nodes become involved;[6] the condition is even more chronic and more apt to develop serious sequelae. The formation of a stricture may develop to the stage of necessitating surgical intervention. Rectal involvement in the male occasionally occurs and this probably is due to a spread of the infection to the posterior urethra and the prostatic utricle. The lymphatic collectors of this region drain into the "posterior lymphatic pedicles" of the prostate gland and from there the infection could reach the "rectal absorbent pedicles."[10] Another possible origin of a rectal lesion may be a direct inoculation of the virus through abnormal practices.

The disease as seen in the female, due to the difference in the lymph drainage in the two sexes, usually takes on a quite different aspect. An inguinal localization, while it may occur, is rather rare. The process is more prone to spread to the deeper pelvic nodes and to the lymph nodes around the lower part of the rectum, due to an inoculation of the virus upon the posterior surface of the vaginal mucosa or the posterior lip of the cervix. Many lymph vessels lead from this region posteriorly through the fascia of the rectum and uterosacral network to the rectal wall, and drain into the lymph nodes about the rectum to a height of 4 to 6 cm. The infection, as a rule, leads to lymphatic stasis and inflammatory rectal stricture. The lesion is often associated with the formation of one or more fistulas. Such rectal strictures in the majority of cases occur in colored women (see Fig. 1).

Primary infection, according to Bernstein,[7] at the vulva or perineum may set up an extensive edema and induration between the vulva and anus. Ulcerations, fibrosis, and various fistulas may follow. (See Fig. 2.)

Unusual cases of extragenital infections have been recorded in literature by Curth,[11] Elitzak,[8] and Hellerström, quoted by Cole.[5]

The diagnosis in the male is usually easy to make. A positive Frei test, when properly interpreted, is most helpful. Like the Wassermann reaction, it may not be related to the present illness. Of important consideration is a history of fleeting initial lesion of the genitalia, followed by an involvement of the inguinal glands of chronic type; bluish discoloration and stretching of the skin, and later the formation of multiple fistulas. In the female, there is in addition to the infrequent inguinal involvement the obstinate chronic ulceration of the vulva associated with elephantiasis (esthiomene) and sclerosis of the vulva, the anal region, and the rectal wall, the latter involvement

producing anal fistulas and rectal strictures. Fournier, who considered the rectal involvement the main feature of the syndrome, described it in 1875 under the name of syphilome anorectal, and thought it was due to the early tertiary stage of syphilis. (Figs. 1 and 2.)

The prognosis of lymphopathia venereum is as a rule good, although the duration of the disease is quite long. However, should the anorectal syndrome present itself, the prognosis becomes grave. The patient becomes an invalid and in some cases death results.

## DIFFERENTIAL DIAGNOSIS

Lymphopathia venereum should be differentiated from chancroidal and syphilitic lymphadenitis, adenitis due to tuberculosis or pyogenic infections, Hodgkin's granuloma, and other malignant growths.

*Chancroid.*—In case of chancroidal bubo there is a definite genital lesion preceding the bubo. The inguinal swelling is more acute and painful than the lymphogranulomatous adenitis. On breaking down of the gland, a single large sinus is formed, while the suppurating "climatic" bubo forms multiple sinuses. Furthermore, one may demonstrate the Ducrey bacilli and a test with chancroidal pus[12] would be positive.

*Syphilis.*—The enlarged lymphnodes are firm, discrete, painless, and usually do not break down. Dark-field examination of the initial lesion and the Wassermann test will aid in diagnosis.

*Hodgkin's Disease.*—The adenopathia is not confined to the inguinal region. There is no tendency of suppuration. Histologic study will be helpful.

*Tuberculosis.*—There is caseation rather than pus in the gland. The histology is quite characteristic. One usually will find a tuberculous lesion in other parts of the body.

## PATHOLOGY

When affected glands are removed by surgical excision, the excised mass is composed of glands of various sizes matted together by periglandular inflammation. On section, recently involved glands show only congestion and reddening, while glands at a more advanced stage show multiple intraglandular abscesses of variable size. The pus contained in these abscesses is whitish, thick, and viscid.

After observing the histologic picture in a fair series of our cases, it is believed that the histology of the lymph nodes is suggestive but not definitely pathognomonic of the disease. It is not proposed here to deal with the histology in detail. It may be stated, however, that we have not found the microscopic appearance as uniform as it is usually reported.

The usual microscopic picture noted was a pregranulomatous or granulomatous type of lymphadenitis as follows: The follicular structure is often moderately obliterated, but it is not unusual to see sec-

tions of the glands with hyperplastic germinal centers. Several areas of fibrosis are present. The sections are studded by tiny abscesses, mainly filled with polymorphonuclear leucocytes. The micro-abscesses may present a central necrosis which contains some pyknotic cells. A hyperplasia of the reticulo-endothelial elements is evident about the abscesses. Collections of lymphocytes and plasma cells are equally conspicuous. Groups of giant cells also may occur (Fig. 3).

Somewhat less frequently one meets with another group of sections of the enlarged lymphglands which may be designated as fibrosing or

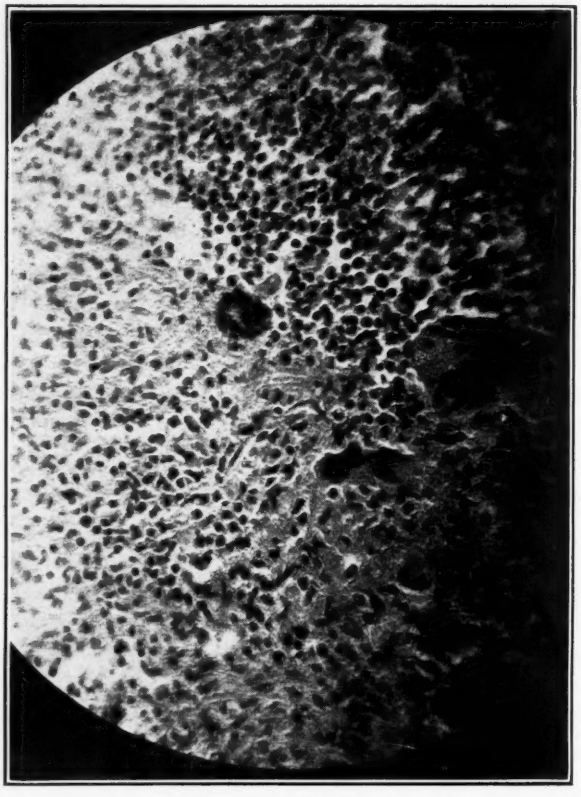

Fig. 3.—Photomicrograph, high power view. Case H. H. Clinical diagnosis: lymphopathia venereum; Frei test: positive. This section of the removed inguinal bubo presents a subacute, granulomatous lymphadenitis. The upper one-third shows a focus of pus cells with some mononuclear cells. Below this lesion toward the right, four giant cells are conspicuous. Left middle zone shows epithelioid cells in a somewhat palisading arrangement. The follicular lymph node structu.e was fairly well maintained.

sclerosing type of lymphadenitis in which giant cells, epithelioid cells, and other signs of a granulomatous lesion are practically absent. There is a very prominent fibrosis instead. However, here also are noted small abscesses and collections of chronic migratory cells (Fig. 4).

In our series of 48 cases of lymphopathia venereum, histologic studies were made on inguinal lymphnodes in 15 cases:

TABLE I

ANALYSIS OF HISTOLOGIC FINDINGS

| | NUMBER | PERCENTAGE |
|---|---|---|
| Number of inguinal bubos studies | 15 | |
| Cases with findings consistent with lymphopathia venereum | 15 | 100.00 |
| Cases indicating a granulomatous lymphadenitis | 10 | 66.66 |
| Cases revealing a sclerosing type of lymphadenitis | 3 | 20.00 |
| Borderline cases* | 2 | 13.33 |

*Two of the cases manifested a subacute lymphadenitis with minute abscesses, but would not fall readily in either of the two preceding groups.

Fig. 4.—Photomicrograph, low power view. Case R. V. Clinical diagnosis: lymphopathia venereum; Frei test: positive. Above section of the removed, enlarged inguinal gland indicates a fibrosing or sclerosing type of lymphadenitis. A broad central zone of the photograph illustrates the pronounced fibrosis. Blood vessel at *A* shows marked chronic endangeitis. About the fibrous area there are rows and groups of plasma cells, endothelial cells, fibroblasts, and various leucocytes. Considerable capillary vascularization is visible towards periphery. Follicular lymphnode structure was mostly obliterated.

## THE FREI TEST

It was not until 1925 that a diagnostic test became available for this disease. Frei at that time made the discovery of an intradermal test, which has since then been known as the Frei test.[3] The Frei test opened a new field for research and aided in the certain diagnosis of

the disease. The technique of the test is simple. The Frei test is performed with an antigen containing the heated virus of the disease. There are three main sources of the antigen: (a) pus aspirated from a bubo, (b) macerated material from diseased gland, (c) brain of a susceptible animal inoculated with the virus.

The pus is obtained by sterile puncture of an unopened fluctuating bubo from a patient having lymphopathia venereum and free from a chancroidal infection, syphilis, or tuberculosis. The pus should be as free from blood as possible. It is diluted with sterile, physiologic salt solution 1 to 5, to 7, or 1 to 10, depending upon its thickness. It is then shaken ten to fifteen minutes, with glass beads if necessary, to facilitate a proper emulsion. The material is heated for two hours at 60° C., and the next day for one hour at 60° C. (In our experience when this order was reversed, i.e., the emulsion was heated for one hour the first day and two hours the next day, it made no difference in the potency of the finished antigen.)

Prior to the acceptance of an antigen, sterility tests should be made, according to Frei,[13] both of the fresh and heated material, under aerobic and anaerobic conditions at thermostat (37° C.) and room temperature. One should realize that the material from the softened bubo is an excellent nutritive medium for microorganisms if not kept sterile. If the material is used longer than three months, the tests should be repeated. The antigen, as a rule, becomes inert after nine months. The antigen before it is released should be tested upon known Frei positive patients and on individuals who are free of lymphopathia venereum.

Antigens prepared by means of maceration of the diseased gland have been used. We have prepared antigens by crushing the excised glands and found the potency of such antigens relatively weaker. Perhaps the concentration of the virus is lower in the firm gland than in the pus formed in the necrotic gland. It is more likely, however, that our method of emulsifying the removed gland was rather crude. Gray[14] describes the preparation of satisfactory antigens from excised glands which were ground by shaking with sterile glass beads in approximately five volumes of sterile saline solution.

Emulsion of the brain of monkeys or mice inoculated by the virus of the disease has been used as an antigen. We have no personal experience with this type of antigen. The experiments of Strauss and Howard[15] indicate that "irrespective of whether the mouse had been infected with lymphogranuloma inguinale or not, an antigen made from the brain of a mouse may induce a reaction similar to the Frei reaction when injected intradermally." "For these reasons," the authors conclude, "Frei antigens made from mouse brain would not

appear to be suitable for routine diagnosis of lymphogranuloma inguinale." Grace and Suskind,[23] on the other hand, have recently reported their results with an antigen prepared from mouse brain through repeated passages. The authors have found this antigen in considerable number of tests as specific and as sensitive as the most potent antigen prepared from human material.

The technique of the Frei test consists of intradermal injection of 0.1 c.c. of the antigen. A tuberculin syringe is suitable. An area of skin with relative freedom of hair should be selected, and in females

Fig. 5.—Same patient as shown in Fig. 2, demonstrating marked reaction and necrosis following use of Frei antigen sixteen days after test was made (dilution 1 to 8 as employed for diagnostic purpose). This readily demonstrates our preference for the thigh as a site better suited for the intradermal test in females. Such marked reactions are infrequent, but they do occur.

the thigh is preferable to the arm in order to avoid a possible necrotic lesion on an exposed surface (Fig. 5). We have been reading the reaction, not only after forty-eight hours, but following the recommendation of Vander Veer,[9] also after the third and fourth days. That this is a good rule to follow was proved to us by the no means infrequent cases that apparently were positive after forty-eight hours and that gave a negative reading after the fourth day. We also have

seen in occasional instances that the reaction became more marked on the third and fourth days. A positive Frei test indicates an allergic state of the skin of a patient who has been sensitized by the virus of the disease either recently or at some occasion in the more distant past. One should read the Frei reaction in front of a good source of light. A positive reaction is denoted by a definitely palpable red papule at least 0.6 cm. in diameter.[16] A large erythematous halo about the papule is common. Care should be exercised not to measure the diameter of the zone of erythema in place of the papule. Uniform readings are difficult to obtain with an ordinary rule; the use of a small steel caliper with one fixed and one sliding jaw* eliminates this difficulty. Undoubtedly the essential point in reading the Frei reaction is whether it is positive or negative; however, a simple scale, such as the following, may be adopted:

A papule, 0.6 to 0.9 cm. in diameter equals positive.

A papule, larger than 0.9 cm. in diameter, which may or may not show a central necrosis, equals strong positive.

A papule, 0.5 cm. in diameter, equals weak positive (doubtful reaction) (see Fig. 6).

Marks of pronounced positive reactions will persist for a long time. In one case of esthiomene, the sites of reactions from four different Frei antigens showed ulcerations and were still covered by crusts four months after the intradermal inoculations. According to Sullivan and Ecker,[17] the present test dose of the Frei antigen far exceeds the necessary amount. His statement may be substantiated to some extent by our findings when we used a 1 to 30 dilution and obtained a Frei reaction of much the same intensity as results from the usual antigen 1 to 7 dilution.

The Frei reaction is definitely specific. A single negative reaction does not rule out lymphopathia venereum. The Frei test will not be found positive until a period of three to eight weeks has elapsed from the time of infection. A temporarily negative Frei reaction may occasionally be present, due to cutaneous anergy in certain cases of prolonged or relapsing lymphopathia venereum with lessened general resistance. Other reasons may be concurrent, early florid syphilis; chancroid, active tuberculosis; or high fever; also an occasional case of gonorrhea.[4, 9, 24]

False positive Frei reaction may result from an antigen contaminated with bacteria. Another reason is suggested in the following statement of Gregoria:[18] "Specific sensitizations may coexist with other diseases, syphilis for instance, and give rise to apparently nonspecific reactions in those diseases."

*Available through most of the laboratory supply houses.

False positive Wassermann reactions of fleeting character may occur in early cases of lymphopathia venereum. We have observed gradually subsiding positive Wassermann reactions in three cases of lymphopathia venereum.

To enhance the specific character of the Frei test, the following steps are suggested:

1. Use three or more Frei antigens, deriving from different sources, simultaneously on each case.

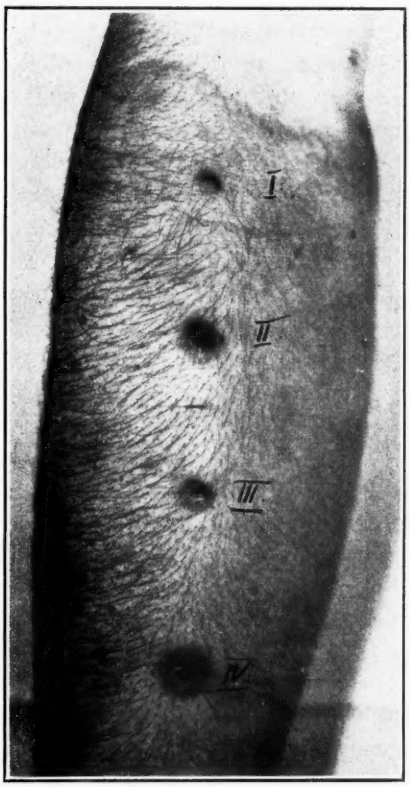


Fig. 6.—Illustrates Frei test in case of C. H. Readings: I = 0.55 cm. (weak positive); II = 0.85 cm. and III = 0.7 cm. (positive); IV = 1.1 cm. (strong positive). Patient was a white male, aged twenty years, admitted to hospital Feb. 3, 1936, complaining of swelling in left groin. Onset Nov. 30, 1935, with pain and soreness left inguinal region followed by gradual swelling to size of lemon. Became fluctuant and Dec. 11, 1935, was incised (elsewhere). Incised wound refused to heal, and on admission to this hospital Feb. 3, 1936, there was an area of swelling in the left inguinal region size of lemon with a two-inch incision draining a small amount of seropurulent discharge. The area is only slightly elevated but is markedly indurated and discolored a slight bluish color. Frei test positive. Kahn three plus and Wassermann strongly positive on two examinations. (Penile lesion denied.) Antisyphilitic treatment did not effect any change of the inguinal adenitis. On Feb. 17, 1936, began intradermal injections of diluted Frei antigen every five days with definite response within two weeks. Initial dose 0.05 c.c., increased 0.05 c.c. at each treatment. Total treatments required were eight in number. Discharged from hospital March 8, 1936. Diagnosis of lymphopathia venereum and syphilis tertiary was made.

2. A papule, less than 0.6 cm. in diameter, should not be regarded as definitely positive.

3. The use of the described caliper is recommended to eliminate the possible fallacy of interpreting a 4 to 5 mm. papule for 6 mm.

4. Make readings after the third and fourth days.

At the Norfolk Marine Hospital we have simultaneously employed three to six proved Frei antigens in each of our cases. Occasionally, we were confronted by peculiar reactions: One antigen would give a positive reaction while the other antigens yielded negative results, and vice versa. Nevertheless, all but one of these instances were taken as indications of cases of lymphopathia venereum. Our stand was borne out by clinical and histologic findings. The probable reason for the apparent discrepancy is that there are at least two subgroups of the disease called lymphopathia venereum. Is it not likely that an antigen prepared from a case of Group I will give a doubtful or negative reaction on a patient of Group II? Perhaps it is not without significance that in some cases the disease produces a granulomatous histologic lesion, while in other cases fibrosis is the predominating lesion. (Other possibilities are that the described variation in the histopathology is dependent upon the stage of the disease or due to effects of treatment.)

Coutts and Bianchi[19] express a somewhat similar opinion, stating that the so-called lymphogranuloma inguinale is the collection of two different diseases, due to two different viruses.

## TREATMENT

Numerous therapeutic agents have been used in the treatment of lymphopathia venereum with varying and not always encouraging results in the hands of different workers. One should not lose sight of cases in which the disease ends by spontaneous healing. Perhaps the best means to evaluate the result of the treatment employed is its ability to shorten the period of invalidism caused by the inguinal adenitis and other lesions. The average duration of the adenopathia may be placed at three to four months. Mild or severe cases with considerably less or longer duration are not uncommon. In those cases presenting inguinal bubo, surgical excision, roentgen ray therapy, and Frei antigen subcutaneously have been tried. Aspiration of the fluctuating gland has frequently been done when sinus formation was imminent. Weekly injections of tartar emetic have been tried. In some cases where tartar emetic has failed, antimony thioglycollamide has given results. In a few of our first cases tartar emetic solution was used and was not attended with good clinical results. Recently we have gained the impression that x-ray therapy deserves further trial. When surgical extirpation of the involved gland is contemplated, it is well to remember that total removal of the gland is sometimes followed by an elephantiasis of the genitalia.

Hellerström (Stockholm)[25] advocates that lymphopathia venereum should be treated in the early stage if a favorable result is expected.

A mild case may heal spontaneously. He would treat a well-defined bubo at an early stage by operative removal, and he believes that excision done at this stage will not be followed by elephantiasis. He administered Frei antigen intravenously, 0.1 to 1 c.c. doses, in ten cases of inguinal adenitis and three cases of esthiomene. The results obtained were good except that the strictures and esthiomene were not influenced.

Howard[20] states that in several cases he has used intravenously or intradermally repeated doses of Frei antigen. Following such treatment he has noticed the healing of discharging sinus tracts. Smith[21] writes: "Perhaps the greatest advance in the treatment of lymphogranuloma cases was the intracutaneous injection of Frei antigen." He treated approximately eight cases of suppurating adenitis by incision, followed by intracutaneous Frei antigen combined with antimony and potassium tartarate. The incisions healed without difficulty. His method of treatment is inconclusive, however, as one is unable to tell which therapeutic agent effected the relief.

The use of Frei antigen as a vaccine in the treatment of lymphopathia venereum was not familiar to us in November, 1935, when we began this type of treatment at the Norfolk Marine Hospital. We decided upon the intradermal administration of the vaccine as a route more effective than subcutaneous or intravenous treatments. The skin is a remarkable medium to take up immunizing properties. It is believed that the intradermally injected virus of lymphopathia venereum creates a depot from which the immunizing agent is slowly and gradually released.

P. A. O'Leary expressed a similar view at a recent staff meeting of the Mayo Clinic.[10] He believes in the therapeutic value of Frei antigen, especially in early cases and given intradermally instead of the subcutaneous route.

It is thought that such vaccine treatment would develop an active immunity, owing to repeated and gradually increased doses of the heat killed filtrable virus of lymphogranuloma which is present in pus used for the vaccine. According to a statement of Gray,[22] the indications are that cure results when the patient becomes immune to the virus.

We found the sterile and potent Frei antigen, diluted four times, an effective agent in treatment of lymphopathia venereum. The resulting vaccine has been a 1:24 or 1:28 dilution of the heat treated pus in physiologic salt solution. This diluted Frei antigen is the only type of treatment received by our lymphogranuloma patients, plus occasional lymphadenectomy, incision, and drainage. We administer the diluted antigen on the nonhairy surfaces of the thighs, at intervals of five days. As Hellerström aptly expresses,[25] sufficiently long intervals are necessary to allow for stimulation of antibody formation and to avoid "saturation." The initial dose is 0.05 c.c., which is increased at

each dose by 0.05 c.c. up to the maximum dose of 1 c.c. The treatment is continued until the sinuses heal and the adenopathy subsides; or in case lymphadenectomy was performed, until the wound healed, requiring from six to twelve doses of the pus vaccine. The administration of the larger vaccine doses requires the making of several wheals, i.e., 0.1 to 0.2 c.c.; but certainly not over 0.3 c.c. of the vaccine is deposited with each intradermal injection. Until now we have used autogenous or heterogenous Frei antigen, deriving from a single case for the preparation of our vaccines. We plan to make up our next vaccine from different pooled Frei antigens. It is possible that a pooled vaccine would be even more effective.

In general, the clinical response to our vaccines consisted of gradual reduction in the size of the gland to only a small indurated area within a period of one to two months. The treatment prevented the formation of new fistulas, induced within a week a beginning reduction in the size of the glandular enlargement, and materially shortened the time required to close an operative wound.

Our experience thus far concerns the effect of the treatment with diluted Frei antigen on the external manifestations of the disease, such as inguinal lymphadenitis; but we had very limited opportunity to try the treatment on rectal lesions. In two of our cases fibrosis had already set in, and therefore the results were not very favorable. However, we believe the treatment may be helpful in cases presenting early rectal lesions. An early diagnosis would be made more frequently if in any involvement of the rectum, particularly in the female, we would consider the possibility of lymphopathia venereum.

It already has been stated that a gradually subsiding positive Wassermann reaction in the presence of lymphopathia venereum rather rules out than confirms syphilis. Where there is any doubt whether the inguinal bubo is due to lymphogranuloma or syphilis, we first treat the syphilitic infection. In a few cases the adenopathia rapidly subsided under antisyphilitic treatment, which might suggest that the present condition was due to syphilis and the positive Frei test was only an indication of a past infection with the lymphogranuloma virus. In other cases the antisyphilitic therapy had no effect on the adenopathy, indicating an actual association of two diseases, syphilis and lymphopathia venereum. In this type of case the antisyphilitic therapy was continued and diluted Frei antigen was administered in addition. (See case history of C. H. under Fig. 6.) Vander Veer[9] advises that specific treatment should be given if the Wassermann reaction is definitely positive, but he contends that true cases of lymphopathia venereum often involute during antisyphilitic treatment.

In our series of 54 positive Frei reactions, 6 were in cases not diagnosed lymphopathia venereum. Two gave no history of previous adenitis, 3 stated there had been a swelling in the groin which sub-

sided spontaneously, and 1 showed the presence of a scar in the inguinal region from previous lymphadenectomy.

For the convenience of interpreting results, we have grouped the 48 cases diagnosed as lymphopathia venereum into seven groups:

*Group I.*—Inguinal adenitis subsided spontaneously in 1 case, twenty-two days from the time of beginning glandular enlargement. Glandular enlargement was about the size of a walnut.

*Group II.*—Ten cases were treated with diluted Frei antigen and no operative procedure. Average number of intradermal injections required, 6.08; average number of days for adenitis to subside, 30.

*Group III.*—Ten cases were treated by incision and drainage of fluctuating bubo, and intradermal Frei antigen was administered. Average number of injections required before adenitis subsided, 6.5; average number of days before adenitis subsided, 30.

*Group IV.*—Eight cases had a lymphadenectomy performed, and no Frei antigen was administered. Average number of days required to heal wound, 40.

TABLE II

TREATMENT IN 48 CASES OF LYMPHOPATHIA VENEREUM

| GROUP | NUMBER OF CASES | PERCENTAGE OF ALL CASES | AVERAGE NO. OF DAYS UNTIL LESION SUBSIDED | AVERAGE NO. OF INJECTIONS OF FREI ANTIGEN | MALE | FEMALE |
|---|---|---|---|---|---|---|
| I Spontaneous healing of bubo | 1 | 2.08 | 22 | -- | 1 | |
| II Cases treated solely with Frei pus vaccine | 10 | 20.83 | 30 | 6.08 | 10 | |
| III Cases treated by incision and drainage of fluctuating bubo, plus intradermal Frei antigen | 10 | 20.83 | 30 | 6.50 | 10 | |
| IV Cases treated solely by lymphadenectomy | 8 | 16.66 | 40 | -- | 8 | |
| V Cases which had lymphadenectomy and received intradermal Frei antigen | 8 | 16.66 | 42* | 7.00 | 8 | |
| VI Cases with coexistent syphilis; bubo subsided under antisyphilitic treatment only | 4 | 8.33 | -- | -- | 4 | |
| VII Cases manifesting rectal strictures | 7 | 14.58 | Treatment incomplete | | 2 | 5 |
| Total | 48 | -- | -- | -- | 43 | 5 |

*The majority of these cases manifested a larger sized bubo than Group IV.

*Group V.*—Eight cases had a lymphadenectomy performed and were given intradermal injections of Frei antigen. Average number of injections required to heal wound, 7; average number of days required to heal wound, 42.

*Group VI.*—Four cases were diagnosed as syphilis; had remarkable inguinal adenitis with positive Frei tests. The adenitis subsided under antisyphilitic treatment.

*Group VII.*—This group of cases includes 5 females and 2 males. In each case a rectal stricture was present. One female presented a marked swelling of the labia minora, wartlike growths about the anus, and an ulcer at the fourchette. Frei antigen was not given in the male cases. An average of three intradermal injections have been administered to the female cases, and to date no beneficial effect has been noted. However, no conclusion may be drawn from so short a treatment period. No improvement relative to the stricture already present is anticipated in those cases where the condition is markedly advanced.

In addition to the treatment previously mentioned, all cases received a hot sitz bath twice daily.

Comparing Groups IV and V, it will be noted that the time of healing of the operative wound was practically the same in both groups. However, the majority of cases in Group V manifested a larger size bubo and consequently there was a larger and frequently deeper wound to heal (see Table II).

## SUMMARY

Brief discussion of the nomenclature, distribution, symptomatology, clinical course, and pathology of lymphopathia venereum is given.

The relation of trauma to the disease is briefly discussed.

Practical comments on performance and interpretation of the Frei test are presented.

In 54 cases which gave positive Frei reactions, there were only 3 without characteristic clinical findings and history. Accordingly we have found the Frei test in 94.5 per cent to be specific.

We have noted discrepancies in certain cases when tested by various potent Frei antigens, also some differences in the histologic picture, which seem to support the opinion that there are at least two subgroups of the disease.

The treatment in our 48 cases of lymphopathia venereum is presented. We feel that the use of diluted Frei antigen, administered intradermally, has demonstrated encouraging results and that its use should be continued with further study.*

*Our studies, especially the pathohistologic examinations, were carried out in cooperation with the National Institute of Health, Washington, D. C. No originality is claimed for the histologic classification presented in Table I. It is based on studies which have been conducted at the National Institute of Health.[26]

Acknowledgment is made to the U. S. Marine Hospital, Stapleton, N. Y., and to Dr. William Curth, Columbia University, New York City, for the first two Frei antigens used in our studies.

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# THE CAUSE OF DEATH IN LIVER PERITONITIS

## The Nature of Toxic Substances Produced by the Incubation of Adult Dog Liver

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THIS is an investigation on the nature of toxic substances produced by the incubation of adult dog liver in vitro and the possible rôle such toxins play in the cause of death in so-called "liver peritonitis."

When 100 gm. of dog liver is obtained with aseptic precautions, incubated twenty-four hours or longer, and sterilized by autoclaving, it will be found to contain heat-stable toxins which cause death of the dog when placed intraperitoneally. Death usually occurs within eighteen hours and is associated with profound shock as reported in a previous publication.[1] The immediate pharmacologic effects which usually follow the intraperitoneal introduction of these heat-stable toxins are those of violent stimulation of the sympathetic autonomic nervous system. The blood pressure is elevated, the heart rate is increased, the pupils are dilated and the pilomotor muscles contracted.

In a recent publication[1] we presented experiments which indicated that these toxins are produced by the action of dog liver bacteria upon the liver substance during the process of incubation. Since they withstand autoclaving, it is obvious that they are not heat labile bacterial exotoxins. We believe them to be degradation products of protein putrefaction. Our first experiments were undertaken to investigate the rôle bacteria play in the production of these toxic substances. To test for the presence of substances which stimulate the sympathetics, small amounts of supernatant fluid from preparations of incubated dog liver sterilized by autoclaving were injected intravenously in dogs prepared to record kymographic tracings of the blood pressure. Increase in heart rate, elevation of blood pressure, and dilation of the pupils were considered pharmacologic proof of their presence.

*Experimental Observations.*—We found that preparations of dog liver incubated without taking precautions to prevent bacterial contamination contained substances which produced an inconsistent pharmacologic effect. When samples of supernatant fluid were injected intravenously, there was sometimes an elevation of blood pressure and other signs of sympathetic stimulation. In other instances, the blood pressure was lowered and no signs of sympathetic stimulation were manifested. When, however, the liver to be incubated was removed with

Received for publication, July 28, 1927.

aseptic precautions, the surfaces scalded, and every effort taken to prevent bacterial contamination, the liver digests always contained substances which stimulated the sympathetic nervous system. We found that these substances were produced in demonstrable quantities after twenty-four hours' incubation. Larger quantities were produced on longer incubation and maximal pharmacologic effects were observed when the supernatant fluid from dog liver incubated seventy-two hours was tested. Bacterial smears made of these digests consistently revealed the presence of anaerobic bacteria which we have repeatedly observed are always present in normal dog liver.

Fig. 1 illustrates the effect of injecting the supernatant fluid from dog liver incubated with precautions taken to prevent contamination as contrasted with the effect of injecting supernatant fluid from liver incubated without these precautions.

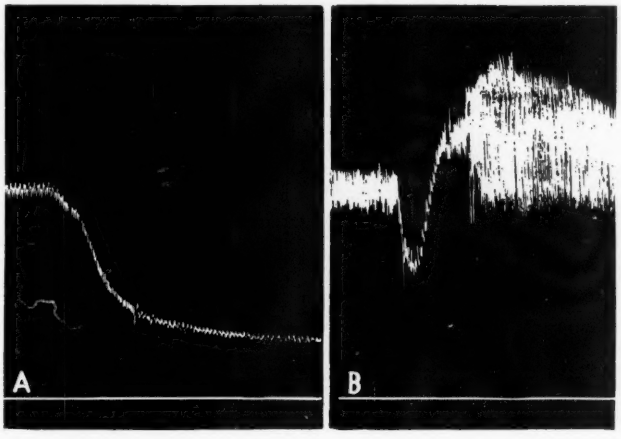


Fig. 1.—The difference between the pharmacologic effects of intravenous injections of supernatant fluid from dog liver incubated with and without contamination by extraneous bacteria. *A*, The injection of 2 c.c. of supernatant fluid from adult dog liver incubated without precautions taken against contamination by extraneous bacteria. This was equivalent to 2 gm. of liver. *B*, The injection of 2 c.c. of supernatant fluid from adult dog liver incubated with precautions taken against contamination by extraneous bacteria. This was equivalent to 2 gm. of liver.

Fig. 1*B* shows that when liver is incubated without contamination substances are produced which cause chiefly a pressor effect upon the blood pressure. We believe these substances are produced by dog liver bacteria acting upon the liver material during incubation. On the contrary, when extraneous bacteria contaminate the liver material, the tendency is for depressor substances to predominate (Fig. 1*A*).

These observations indicate that the production of substances in incubated liver which stimulate the sympathetics depends upon the kind of bacteria present in the liver digests. We further investigated the problem by inoculating preparations of sterile, autoclaved fresh dog liver with a growing culture of bacteria isolated from the dog's liver. When the supernatant fluids from these preparations were tested

after twenty-four hours' incubation, they were found to contain substances which stimulated the sympathetics. We also observed that these substances were produced when autoclaved preparations of fresh dog liver were infiltrated with a growing culture of *Clostridium putrificum*.

After demonstrating that pressor substances were produced by the action of specific strains of bacteria upon the liver material, we were relatively certain that they were putrefactive amines. We believe them to be identical to those isolated and described by Barger and Walpole in 1909.[2] These authors demonstrated that amines with pressor effects upon the blood pressure were formed by the putrefying action of bacteria upon tissue. Later Dale and Dixon[3] reported on the pharmacologic action of such amines. Furthermore, Barger and Dale[4] published an excellent paper upon the chemical structure of amines and their action upon the sympathetic nervous system.

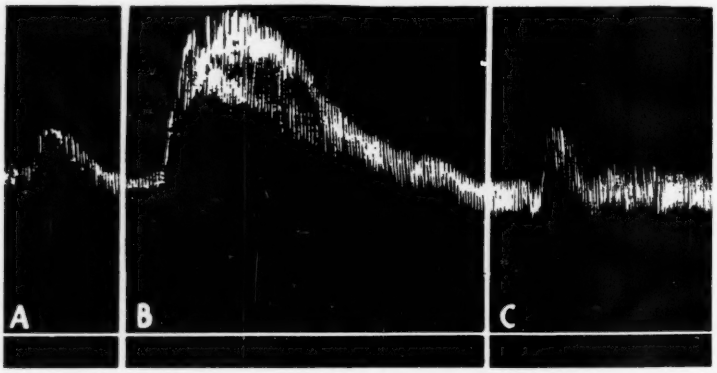


Fig. 2.—The pharmacologic effects of pressor bases isolated from preparations of incubated dog liver (after the methods published by Barger and Walpole[2]). *A*, The injection of 2 c.c. of the fraction containing the pressor base isoamylamine. This was equivalent to 2 gm. of incubated liver. *B*, The injection of 2 c.c. of the fraction containing the pressor base tyramine. This was equivalent to 2 gm. of incubated liver. *C*, The injection of 2 c.c. of the fraction containing the pressor base phenolethylamine. This was equivalent to 2 gm. of incubated liver.

Our next experiments were attempted to identify the pressor substances found in incubated dog liver with the pressor amines isolated by Barger and Walpole.[2] The above authors isolated isoamylamine, tyramine, and phenolethylamine from their preparations of putrid horse meat. Of these three pressor bases, tyramine caused the greatest pharmacologic effect.

Using the methods described by Barger and Walpole,[2] we fractionated the supernatant fluid from incubated dog liver which had been incubated three days and autoclaved.

Fig. 2 illustrates the pharmacologic effects of the substances we isolated. We made no effort to purify the pressor amines to the point of crystallization. The blood pressure tracing shown in Fig. 2 would indicate that the three pressor bases reported by Barger and Walpole[2]

were present. There were also substances present in the supernatant fluid which caused a marked fall of blood pressure. We believe these substances were histamine, peptones, and proteoses.

Mason, Davidson, and Rastello[5] reported that toxic factors were produced from autolyzed dog liver which acted chiefly upon the myocardium and to a lesser extent upon nervous tissue causing an elevation of blood pressure and an increase in heart rate and force of heart beat. We believe that the toxins reported by Mason and others[5] were probably putrefactive amines, chiefly tyramine. We have demonstrated that these pressor bases are rapidly produced by the digestive action of more or less specific strains of anaerobic bacteria which are normally found in adult dog liver. However, it is probable that the amines with pressor effects upon the blood pressure are not the chief toxic factors. We have repeatedly observed that animals subjected to intraperitoneal implantation of incubated liver containing no demonstrable pressor substances die just as rapidly as animals given incubated liver preparations containing the pressor amines. In our opinion, other toxic substances, histamine-like in character, play a more important rôle in the death of these animals. The point we wish to emphasize by these experiments is that bacteria found in normal dog liver will rapidly produce toxic substances when allowed to digest the liver material.

We have demonstrated that when 100 gm. of incubated, autoclaved dog liver are placed intraperitoneally the experimental animal rapidly dies even though the peritoneal cavity remains sterile.[1] The following experiments were carried out to ascertain the rôle played by heat-stable, water-soluble toxins in causing death.

The preparations of dog liver used in these studies were divided into 100 gm. lots, mixed with equal quantities of sterile normal saline solution, and incubated with precautions taken to prevent contamination by extraneous bacteria. All contained both pressor and depressor amines in considerable quantities. After seventy-two hours' incubation, the liver preparations were sterilized by autoclaving and placed in the refrigerator until used.

In the next series of experiments, four 100 gm. lots of sterile, autoclaved preparations of incubated liver were centrifuged. The supernatant fluids containing the water-soluble, heat-stable toxins were filtered off and set aside. From each of two preparations the insoluble sludge was removed and diluted with 100 c.c. of normal saline solution. The different fractions were again autoclaved to insure sterility. Six dogs were used in the experiment. Two dogs were given the supernatant fluid intravenously and two were injected with this fraction intraperitoneally. The two remaining dogs were given the preparations of sludge intraperitoneally. The animals receiving the liver

preparations intraperitoneally were given a preanesthetic of morphine and atropine and subjected to aseptic surgery under deep ether anesthesia.

*Results of Injecting the Supernatant Fluid Fraction Intravenously.*—This fraction contained the heat-stable, water-soluble toxins. The supernatant fluid from 100 gm. of incubated liver was injected into the femoral vein of one animal without anesthesia. The animal struggled violently, the pupils dilated widely, and the heart rate was profoundly increased. Finally, while the last 25 c.c. of fluid were being injected, the animal died with marked convulsive seizures. The other animal was first deeply anesthetized with ether and the femoral vein resected. The supernatant fluid fraction was slowly injected. Even though the animal was deeply anesthetized, the preparation was very stimulating and caused four mild convulsions while being administered. Marked signs of stimulation of the sympathetic nervous system were observed. The heart rate was increased at first but soon became irregular and heart block occurred which lasted twenty minutes. One-half hour following the injection, the animal was able to walk, although the pupils were still widely dilated and the heart rate increased. The animal recovered.

*Results of Injecting the Supernatant Fluid Intraperitoneally.*—The two animals given this preparation intraperitoneally also manifested signs of severe sympathetic stimulation. These symptoms persisted for three to four hours following the injection. Both animals recovered.

*Results of Placing the Insoluble Sludge Preparation Intraperitoneally.*—The two dogs given this preparation suffered no immediate harmful effects. There were no indications that sympathetic stimulating amines were present. However, when examined twenty-seven hours after the injection, both animals were prostrated and in coma. The pulse was weak and thready and the veins were collapsed. They were obviously in an advanced state of shock. One of the animals died twenty-eight hours following the injection of liver and the other survived. Bacteriologic smear and culture taken of peritoneal exudate removed from the animal that died were negative.

In these experiments we made the following observations: The preparation of sludge caused a critical condition of shock which resulted in the death of one animal. The other animal recovered. One dog injected intravenously with the supernatant fluid fraction without anesthesia died immediately with convulsive seizures. When the supernatant fluid was given slowly intravenously to a deeply anesthetized dog, the animal recovered. The two animals injected intraperitoneally with the supernatant fluid were ill for a few hours but both recovered. It is apparent that both fractions are toxic and contribute to the rapid death of animals subjected to intraperitoneal implantation of the unfractionated preparation of incubated liver. It is probable that the

rapid death which follows the intraperitoneal implantation of incubated liver is due in part to the irritating effect of the insoluble material on peritoneal surfaces, causing loss of fluids intraperitoneally. The absorption of heat-stable, water-soluble toxins into the general circulation is also an important factor.

The next experiment was attempted to ascertain the minimal lethal dose of water-soluble, toxic substances found in autoclaved incubated dog liver, when given intravenously to a deeply anesthetized animal. Four animals were given morphine and kept under deep ether anesthesia. Known quantities of supernatant fluid from dog liver, incubated seventy-two hours and sterilized by autoclaving, were added to four 800 c.c. portions of normal saline solution. One of these preparations contained the supernatant fluid from 100 gm. of incubated liver; two contained the supernatant fluid from 200 gm.; and the last contained the supernatant fluid from 300 gm. These preparations were given slowly into the leg veins so that four hours of time were taken for the administration. All four animals manifested signs of marked sympathetic stimulation. The three dogs injected with the supernatant fluid from 100 and 200 gm. of liver survived. The dog injected with the supernatant fluid from 300 gm. of incubated liver died following the intravenous injection of the supernatant fluid from approximately 275 gm. of incubated liver. The terminal event was a marked convulsion.

The experiment demonstrated that the supernatant fluid from dog liver, incubated three days and sterilized by autoclaving, is lethal when given intravenously to a deeply anesthetized dog. The terminal event is marked by convulsive seizures and the supernatant fluid from 200 to 300 gm. of liver was fatal to one animal. We believe that death in this instance was due mainly to putrefactive amines present in the supernatant fluid.

We have reported in a previous publication[1] that 100 gm. of sterile, autoclaved, fresh dog liver will cause a critical state of shock when placed intraperitoneally in the dog. However, these animals will recover, provided the implanted liver substances are not contaminated with bacteria and provided large samples of blood are not removed during the course of the experiment. It occurred to us that if such an animal were subjected to the additional insult of heat-stable, water-soluble toxins produced by the bacterial digestion of liver during incubation, rapid death might be expected to follow. Our next experiment was undertaken to investigate this concept.

Six dogs were used in the experiment. Each of five dogs was subjected to intraperitoneal implantation of 100 gm. of autoclaved, fresh dog liver. Each of two of these animals also received intraperitoneal injections of the supernatant fluid from 100 gm. of dog liver, incubated seventy-two hours and sterilized by autoclaving; while two of them were given this quantity of supernatant fluid from incubated

liver intravenously. The sixth dog was given only the supernatant fluid fraction intraperitoneally. The results of the experiment are given in Table I.

TABLE I

THE EFFECT OF SUBJECTING DOGS TO SIMULTANEOUS INTRODUCTIONS OF AUTOCLAVED, FRESH, GROUND DOG LIVER AND THE SUPERNATANT FLUID FROM DOG LIVER, INCUBATED SEVENTY-TWO HOURS, AND STERILIZED BY AUTOCLAVING

| DOG | PROCEDURE | RESULT |
|---|---|---|
| 64 | One hundred grams of autocaved, fresh dog liver were placed intraperitoneally; at the same time the animal was injected intraperitoneally with the supernatant fluid from 100 gm. of dog liver, incubated seventy-two hours, and sterilized by autoclaving | Died in 40 to 44 hr. |
| 65 | Same as Dog 64 | Died in 32 hr. |
| 66 | One hundred grams of autoclaved, fresh dog liver were placed intraperitoneally; at the same time the animal was injected intravenously with the supernatant fluid from 100 gm. of adult dog liver, incubated seventy-two hours, and sterilized by autoclaving | Died in 14 hr. |
| 67 | Same as Dog 66 | Died in 16 hr. |
| 68 | One hundred grams of autoclaved, fresh dog liver were placed intraperitoneally | Survived |
| 69 | The supernatant fluid from 100 gm. of adult dog liver, incubated seventy-two hours and sterilized by autoclaving were placed intraperitoneally | Survived |

The table shows that neither the autoclaved fresh liver nor the supernatant fluid from incubated liver sterilized by autoclaving caused death. This confirms observations we have made a number of times. When, however, the supernatant fluid from autoclaved, incubated liver containing heat-stable toxic substances is given either intraperitoneally or intravenously to an animal subjected to intraperitoneal implantation of autoclaved fresh dog liver, death results. The experiment indicates that death occurs more rapidly when the supernatant fluid from incubated liver is given intravenously. We can offer no conclusive explanation for this result. However, following intraperitoneal implantation of the toxic amines, it is logical to assume that a certain amount would be deaminized by the liver. Furthermore, it is possible that the autoclaved, fresh liver substance adsorbs part of the toxic material in the supernatant fluid and delays peritoneal absorption so that the life of the animal is prolonged.

The experiment indicates that death of the animals was probably due in part to shock caused by irritation and loss of fluids intraperitoneally. Intraperitoneal absorption of liver protein plus the introduced heat-stable toxins produced in incubated liver were also important factors in causing rapid death.

## DISCUSSION

It has been recognized for a number of years that among the products of protein putrefaction are several amines that have marked power to

stimulate the sympathetic nervous system, causing a rise in blood pressure. The most important of these pressor bases are isoamylamine, derived from leucine; tyramine, derived from tyrosine; and phenolethylamine, derived from phenylalanine. There are also amines derived from amino acids in the process of putrefaction of protein which stimulate nonstriated muscle and constrict arterioles, even though causing a fall in blood pressure. The most important of these bases is histamine, derived from histidine.

All of these amines are derived from cyclic amino acids of proteins by the process of decarboxylization (loss of $CO_2$). It is a debated question whether or not autolysis of protein, unaided by bacteria, can produce these amines. They have all been found in putrid protein material and the general belief is that bacteria are essential for their formation. Furthermore, it has been reported (Hanke and Koessler[6]) that certain strains of bacteria will specifically decarboxylate histidine to form histamine, while others decarboxylate tyrosine to form tyramine, but the same strain will not do both. We believe this observation offers a satisfactory explanation for the observation that dog liver incubated without contamination by extraneous bacteria results in the production of pressor amines (tyramine), while dog liver incubated with contaminating bacteria sometimes contains only substances which depress the blood pressure (histamine). We believe that the nature of toxic amines, whether they are histamine- or tyramine-like in character, depends upon the strains of bacteria acting upon the liver substance. In our experience, a more marked toxemia and shock is caused by incubated liver containing a preponderance of histamine and other substances which depress the blood pressure.

Our experiments have demonstrated that putrefactive amines and possibly other heat-stable substances produced by the action of bacteria upon liver in vitro are very toxic. The supernatant fluid from 200 to 300 gm. of incubated liver killed an anesthetized animal when it was given intravenously. When the supernatant fluid from only 100 gm. of incubated liver was given intravenously to a dog without anesthesia, it caused immediate death. The terminal event was marked by convulsive seizures.

When bacteria act upon protein material outside the gastrointestinal tract, they may produce these toxic substances which enter the general circulation without being detoxified by the intestinal mucosa and liver. We believe that this is probably what occurs when either liver material containing bacteria or incubated, autoclaved liver containing the products of bacterial digestion are placed intraperitoneally in the dog. We believe that these water-soluble, heat-stable toxins are important factors which contribute to rapid death in so-called "liver peritonitis." There are other factors which also contribute to rapid

death. The intraperitoneal absorption of liver protein per se is associated with the loss of fluids intraperitoneally and toxic degeneration of liver, kidney, and adrenal glands.

Dvorak[7] reported that the Berkefeld filtrate of incubated dog liver caused rapid death of the experimental animal when injected intravenously in amounts equivalent to 4 gm. of incubated liver per kilogram of the animal's weight. We have confirmed this observation. However, we also observed that when the filtrate is autoclaved and then placed intraperitoneally it was equally as toxic as when unautoclaved. On the contrary, when the coagulated proteins were removed from the autoclaved Berkefeld filtrate and the resulting preparation placed either intraperitoneally or intravenously, the animal survived. Apparently autoclaving the Berkefeld filtrates rendered them less toxic. This result could have been due to the coagulation and removal of soluble proteins, the destruction of volatile amines, or the destruction of heat labile bacterial exotoxins. We reported[8] that bacteria isolated from the liver and muscle of normal dogs produced no demonstrable exotoxins. However, more or less specific bacterial endotoxins may be important factors contributing to rapid death in liver peritonitis. We are investigating these factors further.

In this paper we have demonstrated that bacteria found in normal adult dog liver rapidly produces toxic amines in the process of incubation in vitro. It is possible that the rapid death of dogs subjected to liver peritonitis can be adequately explained by shock associated with the absorption of putrefactive amines and other split protein products produced by bacterial action on the liver protein in vivo.

## CONCLUSIONS

1. The putrefactive pressor bases, tyramine, isoamylamine, phenolethylamine, and histamine-like substances, are rapidly produced by the action of bacteria upon liver substances during the process of incubation.

2. Whether or not the amines with pressor effects upon the blood pressure predominate over the amines with depressor effects depends upon the kind of bacteria present in the digests.

3. These toxic amines and other heat-stable, water-soluble, toxic substances formed in the process of incubation of dog liver were lethal when the equivalent of 200 to 300 gm. of incubated liver was given slowly intravenously to an anesthetized dog. When injected intravenously into a dog without anesthesia, the equivalent of 100 gm. of incubated liver was sufficient to cause rapid death. The terminal event is convulsive seizures.

4. We have shown that, in addition to other factors, putrefactive amines may also contribute to the rapid death of dogs subjected to liver peritonitis.

5. It is conceivable that deep-seated infections in human subjects may give rise to toxic amines which enter the general circulation and contribute to the shock syndrome frequently associated with such infections.

We wish to express our appreciation to Dr. W. D. Gatch, under whose supervision our investigations originated.

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# LARGE BILATERAL ADENOFIBROMAS OF THE BREAST

## Report of Case in a Girl Thirteen Years of Age

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ALTHOUGH the literature contains several reports of enormous adenofibromas of the breast in young girls, this condition is sufficiently rare to warrant the report of an additional case in which large bilateral adenofibromas of the breast, the larger of the two weighing eight pounds, were present in a girl thirteen years of age.

### REPORT OF CASE

The patient was a girl, thirteen years of age, whose development had been perfectly normal until one year before entry. At that time her breasts began to enlarge, but the development appeared to be normal for her age. Eight months before entry, the breast development had become more marked than the family thought was normal, and the breasts continued to enlarge rapidly and painlessly and became pendulous and burdensome. There was never any discharge from the nipples.

The patient had not menstruated and there was no pubic hair or other evidence of secondary sexual characteristics. During the year preceding our examination, she had gained four inches in height and thirty-five pounds in weight. The family history contained no data relevant to the illness.

Physical examination showed a fairly tall child, the height being sixty-six inches and the weight 125 pounds. She was slightly pale, but appeared to be in good health. There were some dental caries; the tonsils had been removed; the thyroid gland was not enlarged or tender; the heart and lungs showed no abnormality. Rectal examination of the pelvic organs showed no adnexal masses and the uterus, which was infantile, could scarcely be palpated. There was an enormous, nodular enlargement of both breasts (Figs. 1 and 2). They were firm, rounded, and pendulous, hanging to a point well below the umbilicus. The nipples were flattened out and practically invisible. There were many dilated veins over the breasts. Nodular, firm, breast tissue could be palpated well out into the axillae up nearly as high as the clavicles and medially nearly to the sternum.

In view of these unusual findings and in an effort to determine whether there was any endocrine basis for the abnormality of the breasts, a qualitative prolan assay was done by McCullagh's modification of the Friedman test.[1] Urinary estrin was extracted quantitatively with benzol by Koch's method[2] and assayed by a modification of Kurzrok's method,[3] in which variations range from 4.5 to 20 rat units in normal adult women. The Friedman test gave negative findings. An assay for estrogenic substance in two twenty-four-hour specimens of urine showed 26.4 rat units in 1,425 c.c. of urine and 17.6 rat units in 940 c.c. respectively, figures which, by the method of assay used, are within normal limits for adult women. Roentgen examination of the epiphyses at the elbow and hip showed a bone age of approxi-

Received for publication, July 27, 1937.

mately sixteen years and indicated a definite advancement of epiphyseal union. The basal metabolic rate was minus 4 per cent and the blood cholesterol was 171 mg. per hundred cubic centimeters of blood. The Wassermann and Kahn tests gave negative reactions. Examination of the blood showed 4,300,000 red cells, 6,400 white cells, and 78 per cent hemoglobin. Examination of the urine revealed no abnormalities except a faint trace of albumin. The blood sugar was 118 mg. per hundred cubic centimeters three hours postprandial.

A diagnosis of virginal hypertrophy of the breasts with probable adenofibromatous change was made, and bilateral simple mastectomy was advised. In view of the child's age and the size of the breast tumor, it was thought advisable to remove the breasts at two separate operations.

At the first operation, the left breast was removed through a transverse incision which surrounded the nipple elliptically and was carried from the axilla to the sternum. The veins overlying the breast were dilated, but bleeding was easily controlled. The breast consisted of a single, lobulated encapsulated mass of firm, adenomatous-appearing tissue which shelled out of the surrounding tissue easily by blunt dissection. Inasmuch as there was no palpable enlargement of the axillary nodes, the axilla was not disturbed and the muscles were not removed. Three days later a similar procedure was carried out on the other side. The patient stood both operations very well and was discharged from the hospital on the sixth day following the last operation. Both wounds were well healed at this time.

The pathologist recorded the weight of the tissue removed at 3,650 gm. for the left breast, and 2,115 gm. for the right breast. Expressed in pounds the left breast weighed just over 8 pounds and the right breast under 4.7 pounds. The total weight of the tissue removed, therefore was nearly 13 pounds, or approximately one-tenth the patient's body weight. On neither gross nor microscopic examination could any normal breast tissue be identified.

The microscopic examination showed an encapsulated tumor consisting of well-differentiated connective tissue, some of which was quite dense and hyalinized and some of which was very loosely arranged and edematous. Irregularly distributed throughout, there were small and large duct or glandlike spaces lined by cuboidal or low columnar epithelial cells, which had no systematic arrangement. A section which was expected to be nontumorous breast tissue showed loosely arranged fibrofatty tissue, but no epithelial elements. An assay for estrin was made of the tissues removed, but no estrogenic substance was found in this material.*

## LITERATURE

McFarland[4] emphasizes the difficulty of making a histologic differentiation between fibro-adenoma of the breast and normal breast tissue. Of 289 cases which were supposed to be benign, fibro-epithelial tumors, 147 were, on closer analysis, shown not to be tumors as had been reported by the pathologist, but to be either normal breast tissue or breast tissue in some normal phase of involution or hyperplasia. McFarland's conclusion shows the close relationship which exists between fibro-epithelial tumors of the breast and normal breast tissue and raises the question of the influence of the sex hormones on the formation and development of fibro-epithelial tumors.

*The estrin assay on the breast tissue was made by grinding up the fresh tissue and extracting with benzol.

Cheatle[5] states that fibro-adenomata of the breast may be either localized tumors or that they may take the form of a diffuse fibro-adenomatosis affecting the whole breast. He believes there is no difference between the localized and diffuse form in either gross or microscopic appearance. Since fibro-epithelial tumors of the breast so closely resemble normal breast tissue, it is not unreasonable to assume that various endocrine disorders which affect normal breast tissue could likewise play a part in the formation and development of fibro-epithelial tumors of the breast.

Lewis and Geschickter[6] state that they were able to produce changes in the breasts of male monkeys by the injection of estrin in amounts

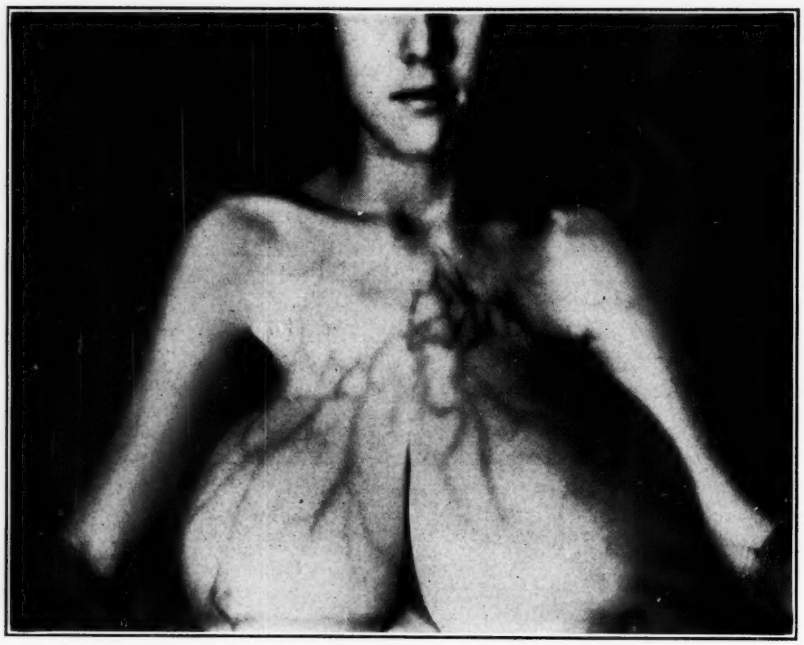

Fig. 1.—Dilatation of veins shown by infra-red technique.

varying from 2,000 to 5,000 rat units. These changes resulted in a condition resembling, but not identical with, gynecomastia. The length of the ducts was increased, the ducts dilated, and there was an increase in the number of epithelial layers. These workers state that there is much clinical evidence to support the view that gynecomastia is due to the action of estrin and quote the case reported by Heidrick in which gynecomastia was associated with a teratoma of the testicle which had resulted in the production of 250 units of the female sex hormone and 3,500 units of gonadotropic hormone per liter of urine. According to Lewis and Geschickter, a localized response of the breast to endocrine disorders leads to the formation of fibro-adenoma, while a general response in one or both breasts causes unilateral or bilateral

virginal hypertrophy. According to these authors this accounts for the clinical fact that fibro-adenomas and virginal hypertrophy are frequently associated.

From their microscopic studies, Lewis and Geschickter[6] believe that the formation of fibro-adenomata is essentially an exaggeration of puberty hypertrophy, that fibro-adenomas, gynecomastia, and virginal hypertrophy may represent different phases of the same process, and

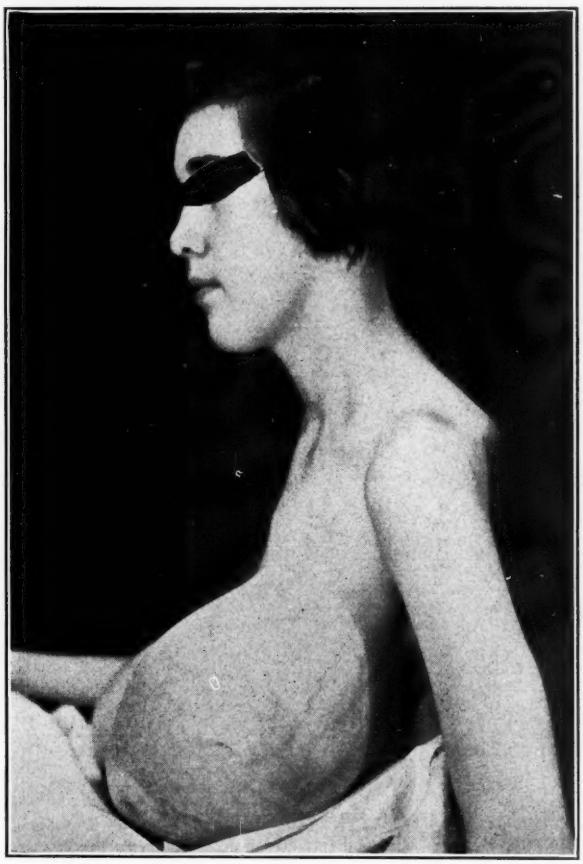

Fig. 2.—Lateral view showing flattening of nipple.

that their development might be dependent upon ovarian hormones. They report the case of a large fibro-adenoma in a twelve-year-old colored girl who had not yet menstruated.[7] The fibro-adenoma contained large quantities of estrin, there being 2,500 units per pound of tissue. Lewis and Geschickter believe these findings indicate that the type of tumor tissue under discussion has a marked capacity to concentrate estrin.

Although the development of large fibro-adenomata of the breast in girls or young women is unusual, a number of cases similar to the

one presented here have been reported. Turner[8] reports two cases of multiple, rapidly growing, soft fibro-adenomata of the breast, one in a girl fifteen years of age and the other in a girl fourteen years of age. In both cases the enlargement commenced at or just after puberty. In both, the enlargement was rapid and excessive and was due to the presence of multiple soft fibro-adenomata. In one case the tumor was unilateral and in the other bilateral tumors were present. Unfortunately no histologic examination was made in the first case, but in the second case the histologic report confirmed the clinical and gross pathologic diagnosis of fibro-adenomata of the breast. The weight of the tumors in both breasts in the fourteen-year-old girl was 15½ pounds. The left breast was larger and weighed 8 pounds immediately after its removal. It is interesting to note that in this case regular menstruation had not been established prior to the removal of the breast tumor. The patient had menstruated once eight months before admittance to the hospital and following this the breasts had begun to enlarge and she had not menstruated again. During this time she had become undernourished and wasted. It is also interesting to note that no normal breast tissue could be recognized. In the first case, that of the fifteen-year-old girl, the patient had menstruated for nearly one year. Only one breast was involved. Three years after the removal of the right breast, a fibro-adenoma developed on the left side and it was necessary to excise the left breast also.

Sellers[9] reports a case of an unusually large fibro-adenoma of the breast in a twelve-year-old colored girl in whom menstruation had not begun. Enlargement of the breast was first noted about three months before entry. The left breast was greatly enlarged and the skin tightly stretched. The overlying veins were dilated, but there was no fixation of the tumor nor were any axillary nodes palpable. A radical mastectomy was performed. The pathologic report was fibro-adenomata of the breast. The weight of the tumor was not given. Later it was necessary to excise a fibro-adenoma of the right breast as well.

Beatson[10] reports a fibro-adenoma of the right breast in a married woman fifty years of age. The tumor weighed six and one-half pounds and had been developing for over a period of two years.

Finsterer[11] reported a fibro-adenoma of the breast in a single woman forty-five years of age. The weight of the breast including the axillary fat was 4½ kg.

Barton[12] described a large fibro-adenoma of the breast in a colored girl seventeen years of age. The weight of the specimen was not given, but the breast measured twenty-seven inches in circumference.

The largest fibro-adenomatous hypertrophy of the female breast which I could find reported in the literature was described by Touraine

and Renault.[13] In this case there was a massive bilateral hypertrophy of the breast with fibro-adenomatous changes. The patient was thirty-six years of age and the enlargement of the breast had begun six years previously, immediately following the removal of the right tube and ovary. The total weight of the tissue removed was 9 kg., 150 gm., or approximately 19.7 pounds.

## DISCUSSION

It is clear from this survey of the literature that large fibro-adenomas of the female breast may develop at any age from before puberty to the menopause and in married women as well as in unmarried women. These tumors are frequently difficult to differentiate, either clinically or by microscopic examination, from the so-called virginal hypertrophy. Although no definite etiologic factors have been demonstrated, it is possible that endocrine disturbances play a part in their development.

The case reported in this paper is unusual as regards the size of the tumor and the youth of the patient.

As McFarland[4] has shown, it is often difficult to determine by microscopic examination whether a section from the breast is breast tissue in a normal state of physiologic hyperplasia or involution, or whether it is a true fibro-epithelial tumor. The presence or absence of a true fibro-epithelial tumor should be determined by gross examination but, in the case reported here, even the gross examination did not conclusively prove whether or not the breast changes were the result of extreme hypertrophy or were caused by the development of bilateral fibro-epithelial tumors. The fact that the masses were well encapsulated, lobulated, and had the gross appearance of a tumor is in favor of their being true adenofibromas, but against this hypothesis is the fact that no normal breast tissue could be identified.

## CONCLUSIONS

1. A case of enormous bilateral adenofibromatous tumors of the breasts occurring before puberty in a girl thirteen years of age is reported. The weight of the left breast was 8 pounds and of the right 4.7 pounds.

2. Assays of the urine showed estrogenic substance in amounts equivalent to that found in normal adult women.

3. Assays of the tumor tissue were negative for estrogenic substance.

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# STENOSIS OF THE LARGE BOWEL DUE TO AMEBIASIS

## Report of a Case Treated by Extensive Resection

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DESPITE the incidence of amebiasis and the undoubtedly frequent occurrence of severe damage to the colon, the surgical literature contains but few instances of extensive colonic resections in these cases. Chatterji[1] says that in rare cases of ulceration of the cecum it may be necessary to excise the cecum and perform an enteroanastomosis. Yeomans[2] reported the case of another surgeon where the transverse colon and splenic flexure were resected for amebic granuloma. This patient died two days later. In Huard's[3] careful presentation of the surgical aspects of cecocolonic ambeiasis, no reference to colonic resection could be found.

The following case report is of interest because of the widespread damage to the colon and because of the improvement following radical excision combined with medical treatment.

Case Report.—S. P., aged fifty-four years, male, was admitted to the Evanston Hospital on April 28, 1935. He had been been under the care of J. M. Garner for a lobar pneumonia since April 10, 1935. About April 21, the patient developed epigastric pain which soon became localized in the right lower quadrant. This was accompanied by gaseous distention and diarrhea. Meanwhile the pneumonia showed definite resolution after April 17. The patient appeared quite ill, and the chief physical finding was a tender mass in the right lower quadrant about four inches in diameter. The temperature was 100° F.; the pulse, 100; and the respirations, 26. The leucocyte count was 37,900; the erythrocyte count was 5,410,000 and the hemoglobin was 102 per cent. The urine was negative. Three stools, examined on April 29 and 30, were negative for amebas, but showed a trace of occult blood.

On April 30, 1935, the mass in the right lower quadrant was explored under the impression that it was an appendiceal abscess. A rather large inflammatory mass involving the cecum was found and an abscess was located above the ileocecal valve and on the posterior mesial aspect of the colon. The abscess was drained after the evacuation of thick green ill-smelling pus. The wall of the cecum at this point seemed to be very friable; in fact, partially necrotic. On May 2, 1935, a definite fecal fistula was established at the abdominal wound. Amebas were found in the discharge from the fecal fistula. The patient had a prolonged and difficult convalescence featured by a period of pyrexia, chills with attention directed to the chest, and an amebic ulceration of the wound borders requiring excision under gas. On May 10 to 12, large ill-smelling necrotic sloughs were passed by rectum. The patient was given two courses of vioform (grains III t.i.d.), from May 17 to 26 and from June 3 to June 21. On June 19, 1935, a proctoscopic examination

Received for publication, July 7, 1937.

(C. E. Pope) disclosed a tubular stricture 7.5 cm. from the anus with total denudation of the mucosa. The patient was discharged from the hospital on June 21, 1935, with a draining fecal fistula but improved in general health.

During the summer months, the patient had considerable difficulty with an exacerbation of the amebiasis, which was treated by a course of emetine, painful excoriation of the wound borders, and arthritis of the left arm and leg. The patient was readmitted to the Evanston Hospital on September 12, 1935. There was now a complete stenosis of the proximal portion of the rectum and the patient experienced considerable pain when the large bowel filled with gas. The erythrocyte count was 4,440,000 and the hemoglobin was 90 per cent. The urine was negative and the stools were negative for amebas.

Laparotomy was carried out on September 13, 1935. At operation (through a left rectus incision) the entire ascending colon, transverse colon, splenic flexure, and most of the descending colon was found to be atrophied down to a hard cord about ¼ to ½ inch in diameter and was apparently devoid of lumen. The sigmoid flexure from the upper end of the rectum to a point half-way up the descending colon, a distance of about 10 inches, was normal. The terminal ileum was implanted, end-to-side, into the most proximal portion of the normal sigmoid flexure. The most distal portion of this sigmoid flexure was then brought out through the lower angle of the wound and the peritoneum and fascia were sutured beneath the loop. Last of all a mushroom catheter was placed by purse-string in the exteriorized colostomy loop. The patient was discharged from the hospital on September 27, 1935, in good condition with a well-functioning left inguinal colostomy and some discharge from the old cecostomy.

The patient was readmitted to the Evanston Hospital on November 21, 1935. His chief complaint was now a severe arthritis, involving the hands, feet, elbows, and shoulders, of some three months' standing. The erythrocyte count was 5,590,000; the hemoglobin, 110 per cent, and the leucocyte count, 10,200. The urine was negative and the stools were negative for amebas. X-ray examination after oral administration of barium showed that there was not complete occlusion of the colon at any point proximal to the sigmoid. The lumen of the transverse colon, however, was narrowed to about ¼ of 1 inch in diameter. The cecum and a portion of the ascending colon also were involved in the contracting process. The stricture between the sigmoid and rectum would not permit the passage of barium.

On November 29, 1935, the patient was again subjected to laparotomy. The transverse colon was found to be narrowed almost to a cord. This narrowing was also present in the ascending colon save for a small portion near the hepatic flexure. The terminal ileum, appendix, cecum, ascending colon, and transverse colon were entirely removed closing the upper descending colon just above the previously performed ileocolostomy. The excised specimen showed chronic ulcers, but no amebas were found in the stained sections. The patient recovered from this operation very satisfactorily and left the hospital on December 10, 1935.

After leaving the hospital, Garner gave the patient a course of sodium cacodylate, as well as an autogenous vaccine. The patient gradually improved and the swelling and pain in the joints subsided. A diet rich in vitamins and parenteral liver extracts was given. In May, 1937, the patient weighed 185 pounds, a gain of 100 pounds from his lowest weight in the hospital. The cecostomy wound had healed entirely. He is now working five hours a day at home and is able to drive his car. He walks around the block three times a day. He still has pain in his joints which diminishes, however, during the day. The colostomy functions well.

The patient takes a heaping teaspoonful of kaolin four times a day and paregoric occasionally. The stools are fluid in the morning but soft in the evening. He changes the colostomy dressing four times daily.

## SUMMARY

A case of widespread damage to the colon from amebiasis is reported. The resultant stenoses and structures were successfully treated by extensive resection of the colon with ileosigmoidostomy plus external sigmoidostomy.

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# DIAPHRAGMATIC HERNIA IN INFANTS; SURGICAL TREATMENT WITH USE OF RENAL FASCIA

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UNTIL very recently, congenital diaphragmatic hernia occurring in infants was not thought to be within the possibility of surgical repair. Hume, writing in 1922, reflected the attitude of the medical profession when he stated that repair of congenital diaphragmatic hernia was not a feasible procedure, and that the most one could hope to accomplish by surgery would be the release of incarcerated or strangulated bowel with no attempt at closure of the defect. Apparently this belief is still widespread, notwithstanding recent successes which prove otherwise.

One of the reasons for the slow development of surgical treatment in the early age group is the erroneous impression that infants do not tolerate extensive procedures within the abdomen or thorax. As a consequence, operations have been withheld until the infants are in extremis, either from intestinal obstruction or from respiratory embarrassment, and attempts at repair have been made under most unfavorable conditions, with very little chance for success. This fault is partly due to the failure to appreciate the difference between defects occurring in infants and those occurring in more mature persons. It is well known that large displacements of intestine into the thorax are occasionally found in individuals living to old age, many of them having no symptoms during life, and being discovered only in routine examination. This has led to the belief that surgical interference should be resorted to only in the presence of severe disturbances of digestion or respiration. This attitude may be acceptable for those making themselves evident after the first years of life, as the changes in this group which indicate surgery are usually slow in their development, and in the early stages of these disturbances the child and adult are better able to withstand the surgical attack. But the situation is quite different in the infant. When it is considered that most cases of congenital diaphragmatic hernia do not live beyond the first few months (Keith,[1] Hedblom,[2] Latta[3]), it is obvious that there must be a different attitude toward this age group. The obstetrician, pediatrician, and surgeon are faced with a situation which requires early recognition and prompt surgical treatment, even in the first few hours of life. The successful cases reported by Johnson[4] on a forty-two-hour-old infant, by Coryllos[5] on a thirteen-day-old infant, and by Orr[6] on a twenty-seven-day-old infant are evidence that early age is not a barrier to operation.

Received for publication, June 24, 1937.

Difficulty in breathing immediately after birth should always suggest the possibility of a defect in the diaphragm. This symptom may moderate after a few days only to reappear in a few weeks or months. Also, there will usually be difficulty with feeding, and failure to gain weight normally. The chief physical signs are small abdomen, displacement of the heart, and absence of breath sounds over the affected side. These findings should suggest x-ray examination with the barium meal, which will definitely establish the diagnosis.

One of the most troublesome technical difficulties in the surgical repair of these cases is the closure of large defects. I have been impressed with this on the two occasions that I have performed the operation. In my first experience, there was a large posterolateral defect on the left side, apparently a persistent pleuroperitoneal canal. An attempt to approximate the edges of the ring was unsuccessful. After placing the abdominal viscera outside of the abdomen to allow more complete exposure of the defect, the renal fascia presented itself as a broad expanse of firm tissue which might be utilized as an aid in accomplishing the closure. By grasping it with forceps it was possible to displace it for a considerable distance cephalad and ventrad and thus attach it to the anterior margin of the defect without undue tension. Since then it has come to my attention that Barrett and Wheaton[7] had previously recommended the use of the renal fascia in the closure of these defects, and from personal communications it would appear that others have also made use of it. That the closure of large defects is often difficult to accomplish is evident from the radical procedures which have been required in some instances. In two successful cases, Bettman found it necessary to fracture the lower ribs and change the convexity of the thoracic wall to a concavity in order to effect a closure. Studies which have been made of the renal fascia indicate that it may, at times, be of inestimable value in this connection and for this reason one who undertakes the repair of a large defect should have a complete knowledge of its possibilities. The mobility and expanse of this tissue is sufficiently great to permit closure of large defects even to the degree of complete absence of a hemidiaphragm.

### ANATOMY OF THE RENAL FASCIA

This fascia is a continuation of the sheath of the psoas major muscle and the arcuate ligament. After leaving the muscle, it extends laterally and downward, its anterior layer covering the anterior surface of the kidney and adrenal gland. After leaving the kidney, it continues laterally as the fascia of the transversalis muscle. It is somewhat thinner over the region of the kidney and adrenal gland than it is over the psoas muscle, but it is nevertheless a definite firm layer of fascia possessing considerable tensile strength. It is loosely attached to the kidney through fibrous strands in the adipose capsule, and the kidney is largely dependent upon it for fixation in its normal position. When

the fascia is displaced upward, the kidney is elevated with it and by this means may be displaced for a relatively great distance, even into the thorax. As the anterior layer of renal fascia approaches the diaphragm,

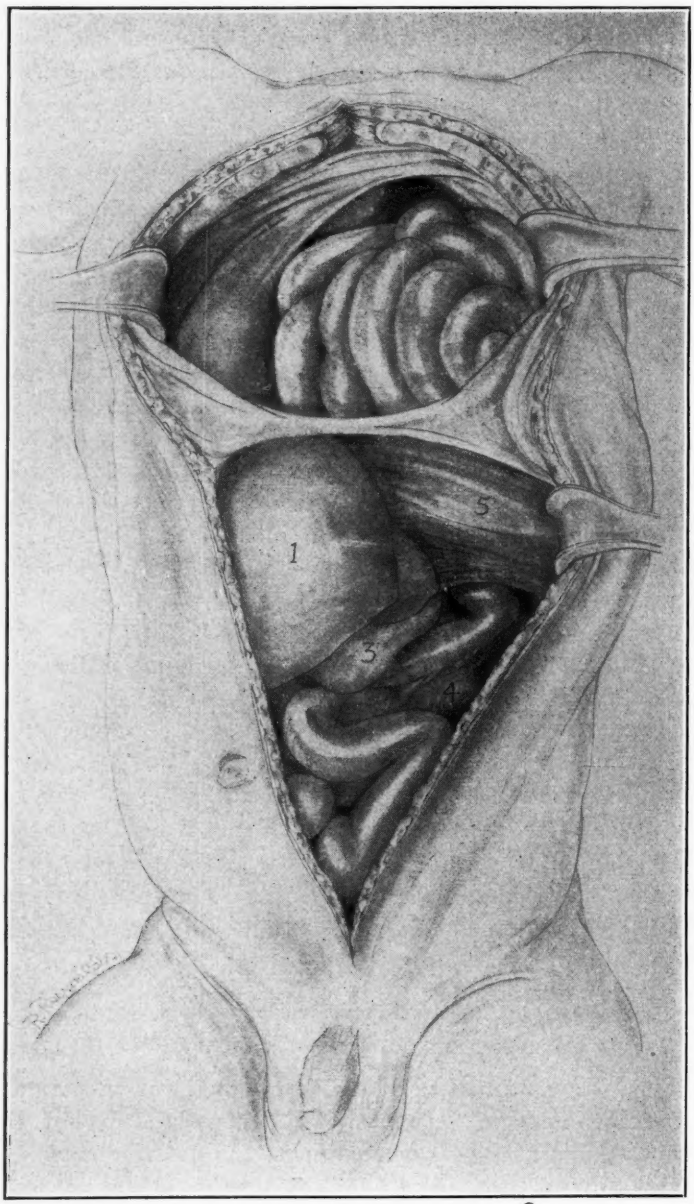


Fig. 1.—Diaphragmatic hernia through the left pleuroperitoneal canal in an infant, aged twenty-eight hours. The spleen and most of the intestines are within the left pleural cavity. *1*, Liver; *3*, stomach; *4*, renal fascia; *5*, diaphragm.

it fuses with the posterior layer and continues cephalad to unite with the fascia of the diaphragm. There are no important nerves or vessels which are intimately connected with the fascia. However, the artery to

the adrenal gland lies in close proximity to the posterior aspect of the anterior layer, and this relationship must be considered in making use of the fascia in the manner to be described later. Further, congenital diaphragmatic hernia which has existed for more than a few days results in extreme distortion of the normal anatomic relationships. The mesentery of the intestine is stretched considerably and the pedicle of the spleen becomes greatly elongated. Because of the latter distortion one

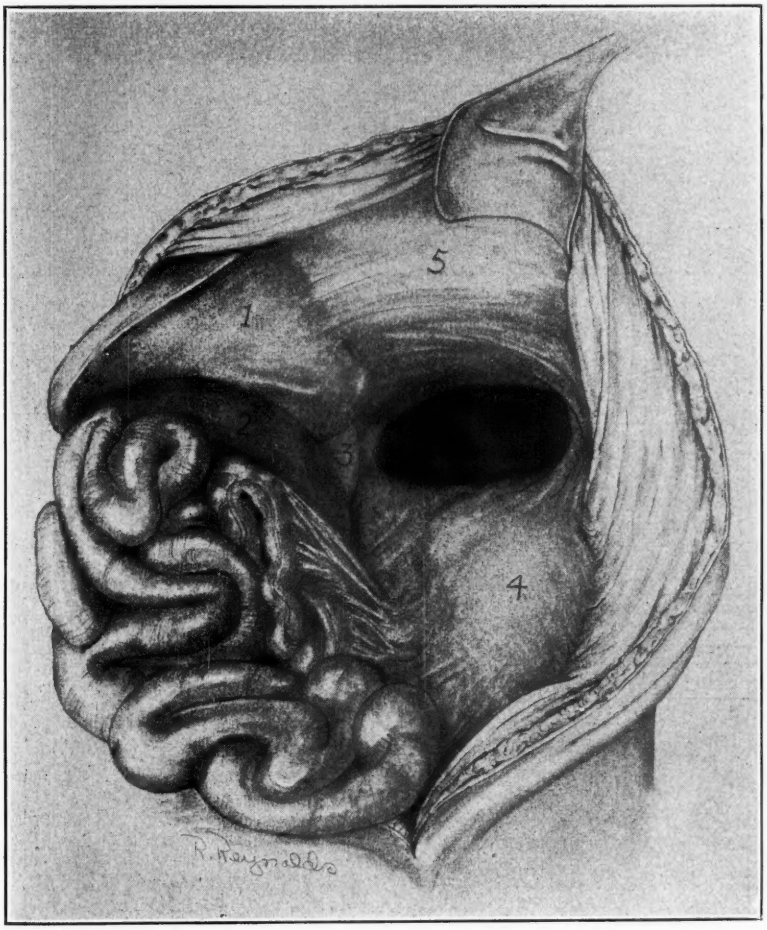


Fig. 2.—Same case as shown in Fig. 1 after displacement of the intestines and spleen from the thorax, showing the defect in the diaphragm and the expanse of renal fascia. *1*, Liver; *2*, spleen; *3*, stomach; *4*, renal fascia; *5*, diaphragm.

may accidentally ligate the lienal artery in suturing the renal fascia to the anterior border of the defect unless the altered relationships are kept in mind.

## TECHNIQUE OF OPERATION

The infant is placed in an anterolateral position, with the head down to lessen the possibility of aspiration of stomach contents during the

course of the operation. A lateral abdominal incision is made along the inferior costal margin from the sternum to the longitudinal muscles of the spine. This wide exposure allows full visualization of the defect in the diaphragm which usually lies posterolaterally. As a general rule the spleen and most of the gastrointestinal tract are within the thorax. These structures are displaced by introducing a rubber tube of about

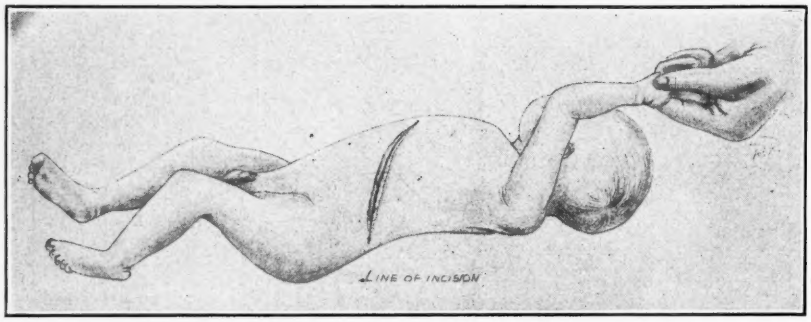


Fig. 3.—Technique of surgical repair, showing line of incision along left costal margin.

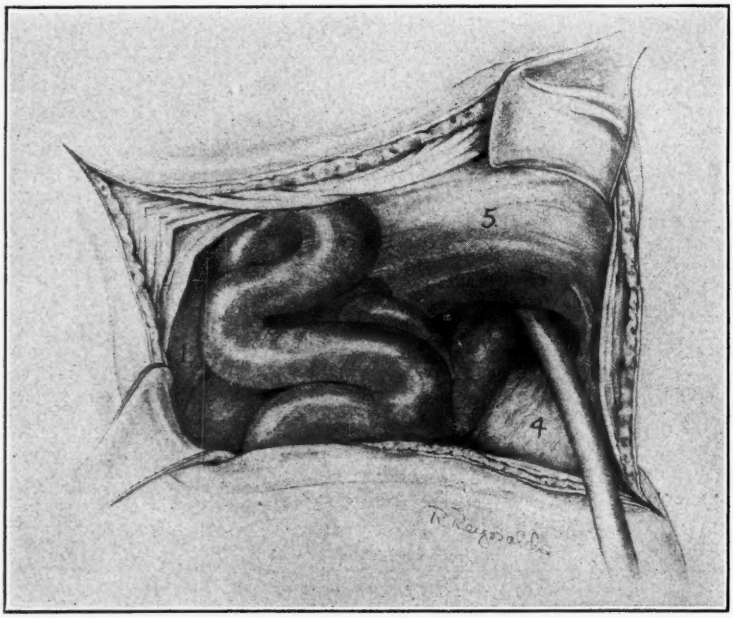


Fig. 4.—Displacement of intestines from the thorax by introduction of rubber tube through hiatus.

⅝ inch in diameter through the aperture, a method suggested by C. H. Mayo.[8] One is impressed by the ease with which the intestine passes from the thorax into the abdomen with this simple maneuver, as compared with the difficulty experienced in reducing the hernial contents without it. The air which enters the thorax through the tube is ap-

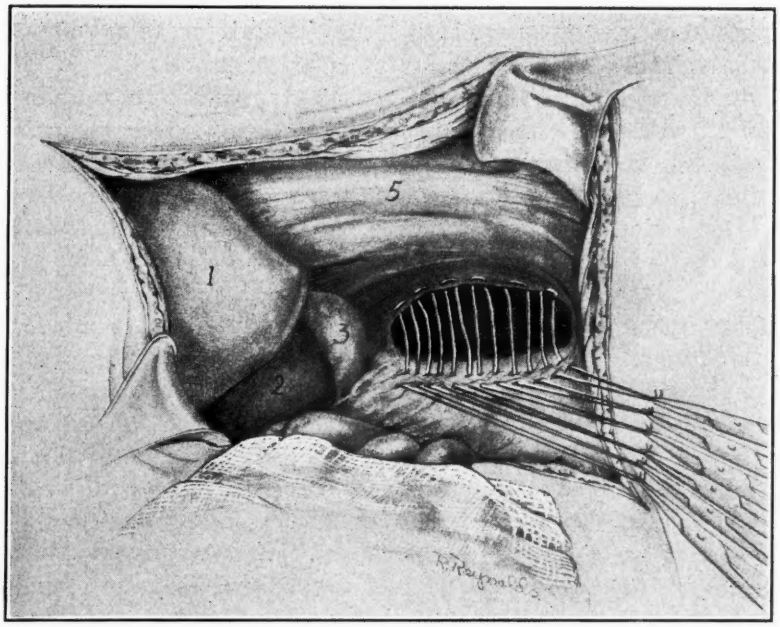


Fig. 5.—Interrupted silk sutures inserted in the anterior border of the hernial ring and in the renal fascia. The intestines, covered with wet gauze, are placed outside of the abdomen.

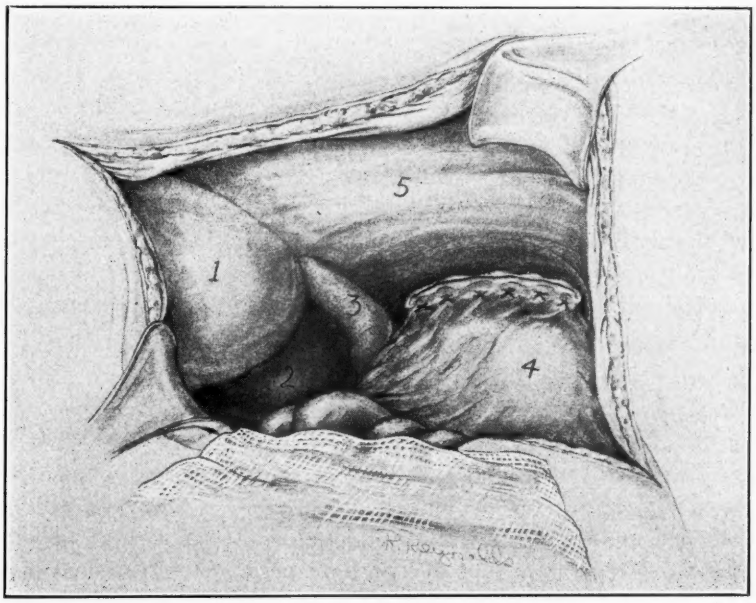


Fig. 6.—Closure of the defect, showing the upward displacement of the kidney which takes place with elevation of the renal fascia.

parently all that is needed to overcome the negative pressure induced by respiration, the force which has caused the suction of the intestines into the thorax.

After the abdominal viscera are dislodged from the thorax, positive pressure anesthesia is started, because the aperture which was more or less closed by the herniated viscera up to this time is now widely open and the already embarrassed lungs and heart may be unable to withstand the sudden increase in atmospheric pressure. The abdominal viscera are now placed in gauze soaked in warm normal saline solution, thus leaving the abdominal cavity empty to facilitate inspection and repair of the defect. Small forceps which will give a minimum of trauma are spaced at intervals of about ¾ inch along the anterior border of the hernial ring in order that they may serve as retractors and also aid in approximating the edges of the defect. The broad expanse of renal fascia which now lies completely exposed is grasped with forceps and raised upward to meet the anterior border of the hernial ring. In the case of relatively small defects it will not be necessary to use the renal fascia. If, however, the defects are extremely large, up to complete absence of the hemidiaphragm, it will be necessary to grasp the renal fascia more caudally and raise it cephalad to meet the thickened anterior margin of the diaphragm which may be its only remnant. Interrupted mattress sutures of No. 9 silk are placed sufficiently close together to assure complete approximation of the edges along the line of closure. Fine silk is preferred for several reasons. It is less irritating; it may be used in much finer size than catgut; and it is more durable and thus is more fitted to withstand the tension of the contracted diaphragm. After the sutures are tied, the intestines are returned to the abdomen, placing them as nearly as possible in their normal relationship without more than necessary manipulation and without consuming too much time. After suturing the fascial layers of the abdominal wall with interrupted 0 chromic catgut, the skin is approximated. Before the infant leaves the operating room, air is withdrawn from the pleural cavity by means of an aspirating needle and syringe. This aids the expansion of the lung by reducing the intrapleural pressure.

### ANESTHESIA

The anesthesia should be administered by one who understands the disturbances occurring with the open thorax. Because of the already embarrassed respiration, the sudden inrush of air with the opening of the abdomen or thorax is especially liable to cause failure of respiration and one must be prepared to use positive pressure anesthesia whenever this danger threatens. Preliminary local anesthesia followed by the maintenance of a mild degree of ether and nitrous oxide general anesthesia is a satisfactory method when used with the rebreathing bag and positive pressure. It is not necessary to use an elaborate apparatus. A tight fitting face mask permits regulation of the intrapulmonary pres-

sure by varying the pressure of the oxygen which is administered with the anesthetic agent. While cases have been operated on successfully without the use of positive pressure anesthesia, it is hazardous to work in the open thorax without this precaution.

### POSTOPERATIVE CARE

The aftercare is directed chiefly toward restoring the normal body fluids, which have become depleted because of difficulty in feeding, and toward maintaining adequate oxygenation. Oxygen inhalation with carbon dioxide or carbon dioxide alone may be needed in the first few days after operation. Water is usually tolerated by mouth within a few hours. The feedings are increased to normal without long delay as starvation is one of the serious features of the disturbance which must be combated early.

### COMMENT

The operation should be performed at an ideal time if possible, and one should not wait for symptoms of obstruction or pneumonitis before advising surgical treatment. As stated before, many cases have been operated upon while the infants were in a poor state of nutrition and suffering from toxic disturbances. It is reasonable to assume that the high mortality which has attended the operation up to the present time is due in part to performance of the operation at an unfavorable time.

I have operated on two patients by the method described here. The first, an infant aged five months, was operated upon in February, 1935. In this case there was a large posterolateral defect in the left hemidiaphragm, apparently a persistent pleuroperitoneal canal. Symptoms of dyspnea and difficulty in feeding had been noticed since birth, but the infant had gained weight until three weeks prior to admission to the University Hospital. At that time he appeared to have a slight cold and there was marked effort in breathing. During the following weeks his weight dropped from thirteen pounds eight ounces to twelve pounds five ounces. Examination showed the heart displaced to the right and breath sounds absent over the left hemithorax. This suggested the possibility of a diaphragmatic hernia, and the diagnosis was established by means of x-ray after barium meal. Operation was performed according to the procedure described above, and the patient made an uneventful postoperative convalescence with the exception of a sharp rise in temperature twenty-four hours after operation. This infant has developed into a normal healthy youngster and shows no signs of any disorder. A recent x-ray examination shows return of the structures in the thorax to the normal position and a normal arrangement of the viscera in the abdominal cavity.

The second case operated on by this technique was that of a baby girl aged eight months. She had shown signs of respiratory difficulty since birth and had failed to gain weight normally. During the first

four months of life she was considered to be a case of malnutrition without known cause. Also, a diagnosis of dextrocardia had been made. At the fifth month x-ray examination was made with barium meal because of the possibility of diaphragmatic hernia, and this revealed the presence of the stomach and intestines within the left hemithorax. Because of progressive loss of weight and dyspnea on exertion to a point of danger, operation was decided upon. Several days before operation she had had an attack of what appeared to be temporary obstruction of the intestine, and for this reason operation was considered all the more imperative. At operation it was found that the left hemidiaphragm was almost entirely absent, being represented by a ring of muscle and fascia at the normal site of its attachment, and by a large thin sac extending to the apex of the left hemithorax. Making use of the renal fascia for the posterior border, and the margin of the rudimentary muscle of the diaphragm for the anterior border, the defect was closed by interrupted sutures. In doing so the size of the abdominal cavity was reduced to such a degree that it was difficult to return the intestines to the abdomen. However, this was accomplished after some effort and the incision in the abdominal wall was closed. The infant appeared to be in good condition immediately after completion of the operation, but in a short time the respirations became very rapid and the temperature rose to 107°, and the infant died about two hours later. An autopsy was not permitted. A complicating factor was present which may have played a part in this death. The operation was performed during a period of extremely high atmospheric temperature, 110° F. on the day of operation. Because of the poor condition of the infant it was not thought advisable to further delay the operation.

## SUMMARY

Most cases of congenital diaphragmatic hernia showing disturbances in infancy do not live beyond the first year of life. For this reason, there must be early recognition and prompt surgical intervention, even in the first few hours, if successful treatment is to be accomplished.

A difficulty which is often encountered in the surgical repair is the closure of very large defects in the diaphragm. This may be overcome by making use of the renal fascia which is ideally suited for this purpose. A technique which involves the use of this fascia is described here.

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# THE EFFECT OF ANESTHESIA ON HEPATIC FUNCTION

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PRIOR to the introduction of methods for determining the status of liver function, the clinician had observed that in the use of certain anesthetics liver damage was to be expected in varying degrees. In 1850, four years after the introduction of chloroform, Casper[1] published reports of cases of death resulting several days after the use of this anesthetic. His observations were later confirmed by others, and during the period from 1850 to 1900 the pathology produced in the liver by anesthetics was thoroughly studied.[2]

Clinical observation, various functional tests, and experimental investigation have demonstrated that certain anesthetics are injurious to the system. A depressed kidney function and a depressed liver function may result from an anesthetic, but this is only an expression of a generalized depression of the cell activity of the organism. The fall in body temperature, which is so well illustrated in the temperature charts of patients following anesthesia, is the reflection of a generalized effect on the body. Oliguria or anuria, depending upon the depth and length of narcosis, is an occasional observation in the surgery ward following the administration of chloroform, ether, and avertin. Following choledochotomy with drainage externally, the surgeon does not become alarmed if the quantity of bile flow is practically nil the first 24 to 48 hours. Mann[3] in 1925 observed the effect of ether on hepatic activity, stating that it resulted in a hyperglycemia dependent wholly upon the liver and that it depressed the secretion of bile. Barbour and Bourne[4] have shown that ether and chloroform always cause a marked blood concentration. A true acidosis[5] which varies in degrees of intensity is produced by avertin and by the inhalation anesthetics. The percentage of hemoglobin is decreased and there is a slight degree of hemolysis. Chloroform increases the coagulation time of the blood, and nitrous oxide, ether, and ethylene decrease the time of coagulation. The central nervous system manifests effects produced by an anesthetic, varying from the subjective symptoms of inability to think and impairment of memory to that of death resulting from nitrous oxide. From these various effects of anesthesia, it can readily be seen that the liver does not by any means bear the brunt of the damage produced.

In order to determine the effect of anesthesia on hepatic function, it is of importance to consider other factors which might influence that organ, or the determined status of function. First, does operative inter-

Received for publication, June 21, 1937.

vention damage the liver? If so, the damage produced occurs simultaneously with the damage produced by the anesthetic, and this factor cannot be eliminated. Second, does the measurement of one function of the liver give a true conception of the damage produced by an anesthetic? The functions of the liver are so numerous that one test cannot pretend to portray the true status of liver function; however, numerous tests relating to specific functions, if properly correlated, will give a fair estimate of the efficiency of the liver. In determining the damage produced by anesthetics, however, all these tests would not be used, for as Soffer[6] has stated: "In testing multiple functions of the liver one positive test is as significant an index of the presence of hepatic damage as would be the case if all the tests were abnormal." Third, if one finds himself in a dilemma regarding which of the various liver functions to measure, he is as equally confused as to which of the numerous tests to select in determining this specific function.

In 1925, Greene, Walters, Snell, Rowntree, and McVicar[9] reviewed the various tests of hepatic function and were of the opinion that the most practical tests were the icterus index, the van den Bergh, and the bromsulphalein dye test. In 1928, Piersol and Rotham[10] considered bromsulphalein to be the most satisfactory dye test. In 1932, Robertson, Swalm, and Konzelmann[11] in a study of the various liver function tests concluded that the bromsulphalein dye test was the most sensitive test. Takane[8] in 1932, working with experimentally produced liver damage, found the bilirubin excretory test (bilirubin injected intravenously) superior to the Congo red excretory test in determining hepatic function. Teneff[7] in 1935 carried out a group of tests on each of a series of patients, and in his experience offered the following tests as the most desirable: glycemic curve after the oral administration of glucose, bengal red dye test, blood bilirubin, and daily urobilin excretion. Soffer[6] in 1935 discussed thoroughly the particular value and indications for each test and offered comparative data indicating that the bilirubin excretory test was the most sensitive of the commonly used tests in determining the excretory function of the liver. The bromsulphalein dye excretory test was the second most sensitive. At the present time, it is apparent that the van den Bergh test, icterus index, and galactose tolerance test are selected for the jaundiced patients by the majority of clinicians, while the bilirubin and bromsulphalein dye excretory tests are selected for the nonjaundiced patients with probable hepatic damage.

Throughout the series of 100 cases to be presented, the bromsulphalein excretory dye test was used, and in the first 18 cases blood bilirubin determinations were obtained at the same time the dye tests were performed. If it could be assumed that no increase in hemolysis of red blood cells takes place during an operation under anesthesia, and an abnormal amount of bilirubin appear in the blood postoperatively, it

would then be apparent that the liver was damaged. This assumption cannot be made, and experimental evidence attests the fact that in order for the blood to show a hyperbilirubinemia, indicating impairment of the function of the liver, a moderately advanced and generalized parenchymal damage must be present. The test was used accepting 1.0 mg. to 3.0 mg. per liter as a normal range of bilirubin values.

The bromsulphalein dye test has proved its merit as a test of liver function, although the same objection may be raised as in the use of blood bilirubin determinations; that is, the liver damage must be extensive before a retention of the dye will occur. This did not contraindicate its use in the series of cases in this study where the test was carried out on the day before operation establishing an estimate of the hepatic function. The dye test was carried out on the first postoperative day and then every other day until the retention was the same or less than the preoperative level. Thus, all patients were followed over an extended period of time and it was possible to gain an insight into the liver damage produced. Soffer[6] stated: "In any particular case that is followed over an extended period of time with an individual test, the results will indicate whether the hepatic lesion is becoming more extensive or is regressing." Five milligrams of the dye per kilogram of body weight were used throughout the series of tests and the blood specimens were collected 30 minutes after the dye administration. A dye retention of 10 per cent or less was considered to lie within normal limits; however, if a preoperative retention of dye was 5 per cent and the first postoperative day retention was 10 per cent, the liver was considered to have been damaged.

In a selection of the cases for this study an attempt was made to avoid those in which suspected hepatic damage existed; however, in a few instances patients were selected who were considered to have had liver damage preoperatively. Excluding Case 13 (long-standing chronic cholecystitis with cholelithiasis)[12] and Cases 16, 17, and 79 (3 patients with pulmonary tuberculosis),[13] the remaining cases of 100 were considered to have had a normal hepatic function. No attempt was made to exclude cases with acute infections, such as appendicitis, pyogenic abscess, and osteomyelitis, for liver damage could not be assumed to be present. With the few exceptions, the patients were not selected, and the observations were made on the patients as they were admitted to the surgical service.

In reviewing the literature regarding the effects of anesthesia on liver function, it was learned that most of the experimental efforts had been carried out in animals; however, these results have been accurate and conclusive in guiding us in a selection of a suitable anesthetic for a given patient. In 1909, Whipple and Sperry[14] observed that two hours of chloroform anesthesia resulted in hepatic damage which required two

to three weeks for recovery. In 1922, LaRocque[16] in a clinical study of the effect of anesthesia on hepatic function arrived at the following conclusions: (1) chloroform always produces liver damage; (2) ether produces liver damage which may be as severe and prolonged as with chloroform, but which differs in that the damage with ether is not as constant as with chloroform; (3) nitrous oxide is the only anesthetic which does not injure the hepatic cells; and (4) nitrous oxide and ether combined reduce considerably the chance of liver damage as compared to ether alone. Sanford, Rosenthal and Bourne[15] in 1928 confirmed the work of Whipple and Sperry and considered chloroform anesthesia to be synonymous with chloroform poisoning. One-half hour of chloroform anesthesia resulted in a hyperbilirubinemia for three days and an abnormal retention of bromsulphalein dye for eight days. Two hours of chloroform anesthesia resulted in a hyperbilirubinemia for eight days and an abnormal dye retention for six weeks. These authors were unable to find definite liver pathology after using ether; however, there was a transient retention of bromsulphalein dye, the degree of hepatic damage paralleling the duration of ether anesthesia. In using nitrous oxide and ethylene with the exclusion of cyanosis, there was no evidence of hepatic damage. With nitrous oxide and ethylene in a closed chamber with poor oxygenation, there was both an immediate and a prolonged abnormal dye retention. Sanford and others concluded that "cyanosis in itself increased the toxicity of an anesthetic on the liver." In 1931, Bourne, Bruger, and Dreyer[17] studied the action of avertin on man and dogs. They came to the conclusion that avertin compared favorably with the inhalation anesthetics relative to its effect on hepatic function. In the human cases there was no abnormal retention of bromsulphalein dye twenty-four hours after avertin anesthesia. In using ether, hepatic function was found to be slightly depressed for twenty-four hours with a return to normal in forty-eight hours. In 1931, Bourne and Raginsky[18] showed that repeated administration of avertin to dogs produced only minimal hepatic damage. In dogs with liver damage previously produced by chloroform, avertin was found to produce a 5 to 30 per cent additional damage. This additional damage disappeared in from twenty-four to forty-eight hours and in no manner affected the total recovery period from chloroform. Takane[8] in 1932, experimenting with rabbits, showed that chloroform produced marked hepatic damage; avertin produced definite liver damage for two days; and nitrous oxide, oxygen, and ether combined were harmless with only a transient retention.

Of the 100 cases receiving an anesthetic for surgery, 49 received nitrous oxide, oxygen, and ether vapor; 27 received nitrous oxide and oxygen; 13, avertin; 8, intraspinal procaine and pantocaine with occasional supplementary nitrous oxide; 2, local infiltration with pro-

caine; and 1, open ether. No attempt was made to include an equal number of patients under each type of anesthesia used; however, these six different anesthetics comprise the types used either individually or in combination as a balanced anesthesia.

Blood bilirubin determinations were carried out preoperatively and postoperatively on the first 18 cases along with the bromsulphalein dye retention test. There was an abnormal bilirubinemia in several instances, but the dye test was so much more sensitive that it was not considered worth while to continue with the blood bilirubin determinations.

Fifty-one per cent of all the patients receiving nitrous oxide, oxygen, and ether vapor showed impaired liver function the first postoperative

TABLE I

THE EFFECT OF ANESTHESIA ON LIVER FUNCTION. ONE HUNDRED SURGICAL CASES STUDIED—GENERAL CONSIDERATION

| TYPE OF ANESTHESIA | TOTAL NUMBER OF CASES | NUMBER AND PER CENT SHOWING DYE RETENTION† | AVERAGE DURATION* OF ANESTHESIA | AVERAGE AGE | AVERAGE AGE WITH DYE RETENTION | AVERAGE AGE WITHOUT DYE RETENTION |
|---|---|---|---|---|---|---|
| $N_2O$ and $O_2$ and ether vapor | 49 | 25<br>51% | Longest, 210 min.<br>122 min.<br>Shortest, 40 min. | Oldest 72<br>33.2 yr.<br>Youngest 12 | 39.1 yr. | 27.3 yr. |
| $N_2O$ and $O_2$ | 27 | 9<br>33⅓% | Longest, 180 min.<br>80 min.<br>Shortest, 30 min. | Oldest 75<br>40 yr.<br>Youngest 16 | 52.2 yr. | 33.9 yr. |
| Avertin | 13 | 10<br>77% | Longest, 210 min.<br>137 min.<br>Shortest, 60 min. | Oldest 58<br>34 yr.<br>Youngest 15 | 39.0 yr. | 19.0 yr. |
| Spinal | 8 | 4<br>50% | Longest, 150 min.<br>99 min.<br>Shortest, 40 min. | Oldest 67<br>48 yr.<br>Youngest 20 | 42.0 yr. | 54.0 yr. |
| Local (procaine) | 2 | 0 | Longest, 40 min.<br>40 min.<br>Shortest, 40 min. | Oldest 34<br>29.5 yr.<br>Youngest 25 | 0 | 29.5 yr. |
| Open (ether) | 1 | 1-100% | 90 min. | 36 yr. | 36.0 yr. | 0 |

*This is the time expressed in minutes with respect to operating time and does not include the time of postoperative narcosis or time during which the anesthetic is exerting its influence after operation.

†In using the expression Dye Retention, it is used synonymously with liver damage.

day with a rapid decline in the percentage showing liver damage at the end of forty-eight hours; however, on the third postoperative day 18 per cent showed a persistent abnormal retention of the dye. By the thirteenth postoperative day the hepatic function in all the cases had returned to the preoperative level. Thirty-three and three-tenths per cent of the patients receiving nitrous oxide and oxygen showed hepatic damage on the first postoperative day with a gradual return to the preoperative level of dye retention by the eleventh postoperative day. Seventy-seven per cent of the patients receiving avertin showed evidence of liver damage on the first postoperative day with an evident prolonged return to the preoperative level of hepatic function in the majority of

cases; however, by the thirteenth day after operation the liver had entirely recuperated from the damage. Fifty per cent of the patients receiving spinal anesthesia revealed evidence of liver damage on the first postoperative day with a rapid recovery from the liver damage by the seventh day. There was no abnormal retention of the dye above the preoperative level in the two cases receiving local anesthesia. In the single case receiving open ether, liver damage resulted with recovery by the fifth postoperative day (Tables I and II).

TABLE II

THE EFFECT OF ANESTHESIA ON HEPATIC FUNCTION RELATIVE TO THE NUMBER OF DAYS REQUIRED FOR THE LIVER TO RECUPERATE FROM THE DAMAGE PRODUCED

| TYPE OF ANESTHESIA | NUMBER OF CASES | NUMBER AND PER CENT OF PATIENTS SHOWING DYE RETENTION ON VARIOUS P.O. DAYS FOLLOWING ANESTHESIA | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | I | III | V | VII | IX | XI | XIII |
| $N_2O$ and $O_2$ and ether vapor | 49 | 25<br>51% | 9<br>18% | 5<br>10% | 2<br>4% | 2<br>4% | 2<br>4% | 0 |
| $N_2O$ and $O_2$ | 27 | 9<br>33⅓% | 5<br>18% | 3<br>11% | 1<br>4% | 1<br>4% | 0 | 0 |
| Avertin | 13 | 10<br>77% | 5<br>39% | 3<br>23% | 2<br>16% | 1<br>8% | 1<br>8% | 0 |
| Spinal | 8 | 4<br>50% | 3<br>37% | 1<br>12% | 0 | 0 | 0 | 0 |
| Ether (open) | 1 | 1<br>100% | 1<br>100% | 0 | 0 | 0 | 0 | 0 |
| Local | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

The duration of anesthesia plays a significant rôle in the hepatic damage produced by an anesthetic (Table III). If the duration of anesthesia does not exceed an hour, only a small percentage of the cases reveal evidence of hepatic damage. This is well illustrated in the cases receiving nitrous oxide, oxygen, and ether vapor, and in the cases receiving nitrous oxide and oxygen, for in these two groups the majority of the cases fall.

Age is an important factor in determining the effect that an anesthetic will have upon hepatic function, while sex does not appear to be a factor (Tables I and IV). The average age of patients showing hepatic damage with nitrous oxide and ether vapor anesthesia was twelve years more than the average age of those patients who did not reveal evidence of liver damage. The cases receiving nitrous oxide and oxygen differed as to the average age by twenty years. In using avertin the average ages differed by twenty years. In the cases receiving spinal anesthesia, the average age with abnormal retention of the dye was less than the average age without retention of the dye.

As previously mentioned, 4 cases were selected because it was considered that hepatic damage existed. In addition to these cases there were 20 other cases revealing unsuspected liver impairment prior to operation. It was an interesting side issue to determine how these livers

TABLE III

LENGTH OF ANESTHESIA IN RELATION TO HEPATIC DAMAGE PRODUCED

| TYPE OF ANESTHETIC | 60″ OR UNDER | | 61″ TO 90″ | | 91″ TO 120″ | | 121″ TO 150″ | | 151″ TO 180″ | | 181″ AND OVER | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NO. CASES | NO. WITH RETENTION | NO. CASES | NO. WITH RETENTION | NO. CASES | NO. WITH RETENTION | NO. CASES | NO. WITH RETENTION | NO. CASES | NO. WITH RETENTION | NO. CASES | NO. WITH RETENTION |
| $N_2O + O_2$ and ether vapor | 7 | 1<br>14% | 16 | 6<br>38% | 10 | 8<br>80% | 4 | 2<br>50% | 8 | 6<br>75% | 4 | 2<br>50% |
| $N_2O + O_2$ | 12 | 1<br>8% | 5 | 2<br>40% | 7 | 5<br>71% | 2 | 1<br>50% | 1 | 1<br>100% | 0 | 0 |
| Avertin | 2 | 1<br>50% | 1 | 1<br>100% | 2 | 2<br>100% | 1 | 1<br>100% | 6 | 4<br>66⅔% | 1 | 1<br>100% |
| Spinal | 2 | 1<br>50% | 2 | 2<br>100% | 1 | 0 | 3 | 1<br>33⅓% | 0 | 0 | 0 | 0 |
| Local | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Open ether | 0 | 0 | 1 | 1<br>100% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

TABLE IV

RELATIONSHIP OF AGE AND SEX IN DETERMINING THE EFFECT OF ANESTHESIA ON LIVER FUNCTION

| TYPE OF ANESTHESIA | NUMBER OF MALES | NUMBER OF FEMALES | NUMBER OF MALES WITH RETENTION | NUMBER OF FEMALES WITH RETENTION | AVERAGE AGE OF MALES WITH RETENTION | AVERAGE AGE OF FEMALES WITH RETENTION | AVERAGE AGE OF MALES WITHOUT RETENTION | AVERAGE AGE OF FEMALES WITHOUT RETENTION |
|---|---|---|---|---|---|---|---|---|
| $N_2O$ and $O_2$ and ether vapor | 31 | 18 | 17<br>56% | 8<br>44% | 40.5 yr. | 36.2 yr. | 27.9 yr. | 26.6 yr. |
| $N_2O$ and $O_2$ | 12 | 15 | 3<br>25% | 6<br>40% | 55.7 yr. | 50.5 yr. | 31.6 yr. | 36.2 yr. |
| Avertin | 7 | 6 | 7<br>100% | 3<br>50% | 46.0 yr. | 28.0 yr. | 22.0 yr. | 17.5 yr. |
| Spinal | 8 | 0 | 4<br>50% | 0 | 42.0 yr. | 0 | 54.0 yr. | 0 |
| Local | 2 | 0 | 0 | 0 | 0 | 0 | 29.5 yr. | 0 |
| Ether (open) | 0 | 1 | 0 | 1<br>100% | 0 | 36.0 yr. | 0 | 0 |

behaved (Table V). Additional liver damage was produced in 8 of the 9 cases receiving nitrous oxide, oxygen, and ether vapor inhalation anesthesia, and in all the cases receiving avertin. The majority of the cases receiving nitrous oxide and oxygen resulted in further impairment of liver function. This group compared favorably with the general group (Table I) as to age and more than favorably as to the duration of anesthesia. The cases showing preoperative impaired hepatic function recuperated from the additional liver damage produced by the anesthesia in an even and gradual decline to return to the preoperative level of abnormal dye retention by the eleventh postoperative day.

TABLE V

THE EFFECT OF ANESTHESIA ON HEPATIC FUNCTION WITH EVIDENCE OF IMPAIRED HEPATIC FUNCTION PRIOR TO THE ADMINISTRATION OF ANESTHESIA: RELATIVE TO AGE, DURATION OF ANESTHESIA, AND DAYS REQUIRED FOR LIVER FUNCTION TO RETURN TO ITS PREOPERATIVE STATUS

| TYPE OF ANESTHESIA | NUMBER OF CASES WITH LIVER DAMAGE PRIOR TO ANESTHESIA | AVERAGE DURATION OF ANESTHESIA | AVERAGE AGE | NUMBER AND PER CENT OF PATIENTS SHOWING DYE RETENTION ABOVE PREOPERATIVE LEVEL ON VARIOUS POSTOPERATIVE DAYS | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | I | III | V | VII | IX | XI | XIII |
| $N_2O$ and $O_2$ and ether V | 9 | 110 min. | 47.2 yr. | 8<br>89% | 6<br>67% | 4<br>44% | 1<br>11% | 1<br>11% | 0 | 0 |
| $N_2O$ and $O_2$ | 11 | 90 min. | 48.0 yr. | 6<br>55% | 3<br>27% | 2<br>18% | 0 | 0 | 0 | 0 |
| Avertin | 2 | 125 min. | 36.5 yr. | 2<br>100% | 1<br>50% | 0 | 0 | 0 | 0 | 0 |
| Spinal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Local | 2 | 40 min. | 29.5 yr. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ether (open) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

In carrying out the postoperative dye tests, it soon became obvious that the majority of those patients who were enjoying a smooth and uneventful convalescence seldom revealed evidence of impaired liver function. On the contrary, if the patient was having marked nausea and vomiting, fever, generally knocked out and below par, his chances of showing an abnormal retention of dye could usually be predicted (Table VI). In 51 patients without abnormal dye retention postoperatively and who had a smooth and uneventful convalescence, 90 per cent were

TABLE VI

RELATIONSHIP OF DYE RETENTION TO POSTOPERATIVE COURSE

| POSTOPERATIVE CASES WITH DYE RETENTION | | | | POSTOPERATIVE CASES WITHOUT DYE RETENTION | | |
|---|---|---|---|---|---|---|
| 49 PATIENTS | | | | 51 PATIENTS | | |
| SYMPTOMS | NO SYMPTOMS | HIGHER RETENTION AFTER 1ST POSTOPERATIVE DAY | DEVELOPED INFECTION | SYMPTOMS | NO SYMPTOMS | DEVELOPED INFECTION |
| 27, or 55% | 22, or 45% | 5, or 10% | 5, or 10% | 5, or 10% | 46, or 90% | 1, or 2% |

classified as being symptom free. In the 49 cases which showed impaired hepatic function by the anesthesia, 55 per cent were classified as having symptoms. No attempt will be made to explain whether the symptoms result from impaired function or vice versa; however, 5 of the cases with symptoms and abnormal dye retention revealed higher retention of the dye after the first postoperative day. This rise in dye retention, after the first postoperative day, is not in keeping with liver damage produced by anesthetics, and in these 5 cases at least, the increased damage must be attributed to the complications. One case had paralytic ileus, one a wound infection with a question of meningitis; one had marked abdominal distention with delirium, one had a severe wound infection, and the fifth case was generally below par without any definite cause for further liver damage after the first postoperative day.

This brings up the rôle of infection commonly encountered in surgical cases and the relation of infection to impairment of hepatic function, exclusive of diseases of the liver and biliary tract. Brochner and Mortensen[19] studied 50 cases with acute febrile diseases in 1934 and 13 cases showed abnormal retention of bilirubin in using the bilirubin excretory test. This test revealed marked impairment of liver function in chronic sepsis. In 4 cases of pneumonia, 1 of encephalitis, and 1 of tuberculous meningitis, hepatic damage was found to be present. Patients with active pulmonary tuberculosis[13] have been proved to have an associated liver damage. In this series of 100 cases the total number with demonstrable preoperative infection was 13. Of the 13, 5, or 39 per cent, revealed the presence of preoperative impaired hepatic function. Eighty-seven revealed no apparent infection, and of this group 19, or 21 per cent, had preoperative liver damage (Tables VI and VII). In the 49 patients with postoperative hepatic damage, 5, or 10 per cent, had accompanying infection. Three had wound infection, 1 a pneumonitis, and 1 an upper respiratory infection. In the 51 cases without liver damage, postoperatively, 1 had a wound infection, and the liver function remained normal as determined by the dye test. The cases without evidence of impaired liver function on the first postoperative day were not followed further, and this no doubt explains the greater frequency of infection in the cases with abnormal dye retention in that the latter cases were followed over a long period of time.

## COMMENT

A series of 100 surgical cases was studied relative to the effect of anesthesia on hepatic function. The suspected cases of hepatic damage were excluded with the exception of 4 cases; however, 20 additional cases of unsuspected liver damage were found to be present in the preoperative series. The bromsulphalein dye excretory test was used throughout, accepting 10 per cent or less as a normal retention. Five milligrams of

TABLE VII

TABLE VII

CASES SHOWING INFECTION—RELATION OF LIVER FUNCTION PREOPERATIVELY AND POSTOPERATIVELY

| CASE NO. | SEX | DIAGNOSIS | AGE | OPERATION | ANESTHESIA | DURATION OF ANESTHESIA | LIVER FUNCTION PREOPERATIVE | LIVER FUNCTION POSTOPERATIVE | REMARKS ON POSTOPERATIVE COURSE |
|---|---|---|---|---|---|---|---|---|---|
| 13 | F | Chronic cholecystitis; c. d. stone | 58 | Choledochotomy, cholecystectomy | $N_2O$ and $O_2$ and local | 120 min. | | I III V VII<br>60% 80% 80% 60% 40% | 1 and 2. Distention, nausea, and vomiting, thereafter O.K. |
| 15 | M | Chronic empyema (rt.) | 20 | Schede T.P. | $N_2O$ and $O_2$ | 60 min. | I<br>10% 10% | | Uneventful |
| 16 | F | Pulmonary tbc. (left) | 24 | 1st stage T.P. | $N_2O$ and $O_2$ | 120 min. | I<br>30% 30% | | Uneventful |
| 17 | M | Pulmonary tbc. (left) | 25 | 4th stage T.P. | $N_2O$ and $O_2$ | 75 min. | I<br>60% 60% | | Uneventful |
| 28 | M | Inadequately drained abscess mediastinum | 25 | I. and D. secondary | $N_2O$ and $O_2$ | 40 min. | I<br>10% 10% | | Uneventful |
| 31 | F | Abscess forearm | 48 | I. and D. | $N_2O$ and $O_2$ | 40 min. | I<br>5% 5% | | Uneventful |
| 43 | M | Chronic osteo rt. femur | 21 | Saucerization | Spinal | 75 min. | | I III V<br>10% 20% 15% 10% | 1. T 102°—anorexia. 3. Same. 5. T 99°, then O.K. |
| 51 | M | Osteo foot | 47 | Sequestrectomy | $N_2O$ and $O_2$ and ether V. | 35 min. | I III<br>5% 25% 5% | | Uneventful |
| 59 | M | Acute appendicitis | 20 | Appendectomy | $N_2O$ and $O_2$ | 40 min. | I<br>5% 5% | | Uneventful |
| 65 | M | Teneosynovitis hand | 34 | I. and D. | Local | 40 min. | I<br>15% 15% | | Uneventful |
| 66 | M | Acute appendicitis | 19 | Appendectomy | $N_2O$ and $O_2$ | 60 min. | I<br>3% 3% | | Uneventful |
| 82 | M | Osteomyelitis of a m p. stump | 58 | Sequestrectomy | Spinal | 40 min. | I<br>5% 5% | | Uneventful |
| 87 | M | Subphrenic abscess | 43 | I. and D. | $N_2O$ and $O_2$ | 85 min. | 15% I III V<br>30% 25% 15% | | 1 and 3. Marked vomiting |

Total no. cases with preoperative liver damage, 24.
Total no. cases with preoperative infection, 13; 5, or 39%, liver damage.
Total no. cases without apparent preoperative infection, 87; 19, or 21%, liver damage.

the dye per kilogram of body weight were given the patient and a sample of blood was taken 30 minutes after injecting the dye intravenously. The test was carried out on the day preceding operation and on the first postoperative day. If there was an abnormal dye retention the first postoperative day, the test was repeated every other day until the dye retention was within normal limits or had returned to the level of preoperative retention.

Avertin produces hepatic damage in a higher percentage of cases and to a greater degree than nitrous oxide, oxygen, and ether vapor anesthesia; nitrous oxide and oxygen; spinal; local; and open ether. The liver is slower in recuperating from the damage produced by avertin than from the other four types of anesthesia which produced hepatic damage. Nitrous oxide and oxygen results in liver damage in a smaller percentage of the cases than nitrous oxide and ether vapor, and spinal anesthesia; however, the damaged liver from nitrous oxide and oxygen recuperates at about the same rate as the hepatic damage produced by spinal, and ether vapor with nitrous oxide. Local anesthesia did not produce liver damage; however, the other five types of anesthetics used produced hepatic damage in varying degrees: avertin is the most toxic to the liver, and in order of decreasing toxicity, nitrous oxide and ether vapor, spinal, nitrous oxide and oxygen, and local anesthesia may be listed.

The longer the anesthesia (avertin, inhalation anesthetics, or spinal), the greater the chance of liver damage.

Sex does not influence the effect of anesthesia on hepatic function. The older the patient the greater will be his chances of hepatic damage from an anesthetic.

If impaired liver function exists prior to the administration of avertin, or nitrous oxide, oxygen, and ether vapor anesthesia, it is a certainty that additional liver damage will result. In the majority of cases where impaired function of the liver exists, nitrous oxide and oxygen anesthesia will result in additional hepatic damage. The impaired liver recuperates from the additional damage due to anesthesia at about the same rate as the normal preoperative functioning liver recuperates from the damage by an anesthetic.

The maximum hepatic damage produced by the group of anesthetics used in this series occurred during the first twenty-four hours postoperatively.

Patients with uncomplicated and smooth convalescence seldom show hepatic damage. If a rise in the percentage of retention of the dye occurs after the first postoperative day, a complication will usually be found to be present.

Excluding infections of the liver and biliary tract, pulmonary tuberculosis, chronic sepsis, and overwhelming infections, surgical cases with

an associated infection such as acute appendicitis, abscesses, and wound infections, will not reveal evidence of impaired hepatic function resulting from the infection per se.

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# CHOICE OF ANESTHETIC AGENTS AND METHODS OF THEIR ADMINISTRATION FOR DIABETIC PATIENTS

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THE selection of the most suitable anesthetic for the patient for whom factors in addition to those arising from the nature of the surgical demands must be considered constitutes a problem worthy of the combined attention of surgeon, clinician, and anesthetist. This is especially true in cases in which the surgical condition is complicated by diabetes mellitus. This type of patient tolerates certain anesthetics well, others rather well, and still others badly. One might employ only those agents which the patient tolerates well, except for the fact that they do not, in all instances, meet the needs of the surgeon.

A consideration of the peculiar problems of the diabetic patient reveals that the greatest danger is acidosis, under the shadow of which he must live his whole life. Paramount in the prevention of this complication are proper diet and facilities for its combustion and adequate elimination. Insulin has afforded a remarkable reduction in the operative mortality among diabetic patients. This has been emphasized by Walters, Meyerding, Judd, and Wilder, who reported a mortality of 3.3 per cent in 2,086 cases in which operations were performed on diabetic patients.

Anesthetic agents, by the very quality which renders them capable of inducing anesthesia, interfere with the normal functioning of the cells which they affect. If the function of the cells of the liver, pancreas, and kidney of a diabetic patient is sufficiently disturbed, acidosis results. If the acidosis is not too severe or of too long duration, and if it is recognized, it can be combated successfully and no permanent damage will result. Thus, its complete prevention is not essential or indeed, in many cases, possible.

Chloroform and ether, when used to produce anesthesia, cause hyperglycemia.[16, 21] Foster said that the increase in the value for the blood sugar coincident with ether anesthesia is probably the result of defective utilization of carbohydrate. Rabinowitch said that ether prevents the conversion of dextrose into glycogen and the storage of the latter in the liver. It also interferes with the metabolism of the

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Received for publication, July 30, 1937.

glycogen already there, and in these ways causes hyperglycemia. This interference, according to Simpson, is attributable, at least in part, to asphyxiation of tissues. Sansum and Woodyatt found that when ether is administrated to phlorhizinized dogs, hyperglycemia results immediately. They explained this on the basis of the transformation of hepatic glycogen to sugar in the presence of asphyxia. Ether diminishes the excretion of urine, and therefore also diminishes the excretion of nitrogen, dextrose, and acetone bodies. Katsch and von Friedrich noted that ether stimulates the external secretion of the pancreas. Joslin and Simpson suggested that, in consequence of this action, it might also diminish the internal secretion of this gland.

Stehle and Bourne expressed the opinion that ether increases the hydrogen ion concentration of the blood and lowers the carbon dioxide combining power of the plasma. In experiments on dogs, van Slyke, Austin, and Cullen found that ether anesthesia always caused an increase in the hydrogen ion concentration in all cases, and an accompanying decrease in the alkaline reserve, which was the result of the introduction of acid into the blood or the withdrawal of base from it. Leake, Leake, and Koehler confirmed the work of van Slyke, Austin, and Cullen and observed that the acidosis which develops is not dependent on the respiratory activities, and therefore is not the result of acapnia. They indicated that the acidosis is more probably due to loss of base from the blood than it is to the addition of acid, as they found no marked increase in the concentration of acetone bodies in the blood during prolonged ether anesthesia. Cullen and his associates found that the larger part of the decrease in alkali reserve which occurs as a result of ether and chloroform anesthesia takes place early in the course of the anesthesia. The occurrence of this decrease together with the prompt increase in hydrogen ion concentration suggests an uncompensated acidosis. Gross said that the concentration of acetone bodies does not tend to increase as a result of anesthesia with ether or chloroform and he did not find any significant increase in the concentration of lactic acid in the blood under these conditions. Blum demonstrated that the hypodermic injection of beta-oxybutyric acid into normal dogs does not cause the appearance of diacetic acid and acetone in the urine, but if the dog is under chloroform anesthesia, a marked acetonuria results. It is a common thing to find acetone present in the urine of nondiabetic patients following ether anesthesia, but this probably is frequently accounted for by semistarvation from restricted intake of food (carbohydrate).

Hagen called attention to the striking similarity between the disturbances of metabolism associated with the acidosis of diabetes and that resulting from ether anesthesia. This similarity includes even the narcotic effects. He expressed the opinion that "a (diabetic) patient free from acidosis, with an ample supply of alkaline salts and water

in the body, a blood sugar within normal limits and in a normal state of nutrition may be considered as good an operative risk as a non-diabetic patient." Wilder agreed with this statement although he excepted those patients who had diabetes associated with arteriosclerosis and who were subjected to operations on the sigmoid colon. In such cases, the danger of leakage from delayed union of the intestine is always present as the blood supply is poor. Joslin emphasized the fact that administration of chloroform interfered with carbohydrate metabolism and that this interference disturbed the metabolism of fat and resulted in acidosis and coma. The concentration of fat in the blood is increased by ether anesthesia. Sansum and Woodyatt found acetonuria following etherization of normal dogs. Ether necessitates fasting before anesthesia and, by causing postanesthetic nausea and vomiting, interferes with the ingestion of food.

Most writers are agreed that ether and chloroform are dangerous anesthetics for diabetic patients.[3, 5, 7, 9, 12, 26] They condemn chloroform altogether and advise avoiding ether if possible, but they admit that it may be safe if used carefully and in small amounts. Fitz said that ether is well tolerated by many diabetic patients but not in those cases in which the diabetes is complicated by sepsis, and not unless a small amount is sufficient. Judd and his colleagues said that ether is the anesthetic of choice for many diabetic patients. They found that the mortality was no higher with ether than with other anesthetics. Ether is not ideal from a medical viewpoint, but, as it produces better anesthesia and relaxation than anesthetic gases alone, it permits a more rapid operation and lessens shock. Lemann did not find any evidence of acidosis in several cases in which ether was administered to diabetic patients. Walters, Meyerding, Judd, and Wilder reiterated the opinion that ether is preferable if it shortens the duration of the operation. The importance of using as little ether and for as short a time as possible is realized by all who recommend its use.[2, 35] According to Fitz, the amount of ether used for 100 abdominal operations at the Mayo Clinic was only 46 per cent of the amount used in a similar series of cases in the average hospital elsewhere.

Mixtures of nitrogen and oxygen cause as much acidosis as nitrous oxide and oxygen. The acidosis is therefore the result of anoxemia. Acetylene acts much as nitrous oxide, but it is more effective and may therefore be used with larger amounts of oxygen and with a correspondingly lessened danger of acidosis.[33] Ethylene behaves as acetylene in this respect. Leake and Hertzman said that if sufficient oxygen to keep the oxygen saturation of the blood within normal limits is used with ethylene (92 per cent or more), no change in the chemical composition of the blood should be expected. These authors found that if there is no anoxemia when ethylene and oxygen are used to anesthetize dogs there is a slight fall in the hydrogen ion concentration

and carbon dioxide content of arterial blood but not beyond normal limits when anesthesia is maintained for half an hour. If anoxemia is present, however, there is an initial increase in arterial hydrogen ion concentration with inconstant changes in carbon dioxide content of the blood. This condition, which persists fifteen to twenty minutes, is followed by a fall in the hydrogen ion concentration and in the carbon dioxide content. It is impossible to maintain nitrous oxide anesthesia without anoxemia, but neither nitrous oxide nor ethylene influences the reaction of the blood so markedly or so rapidly as ether or chloroform.

Local anesthesia is recognized by many as one of the most favorable types of anesthesia for diabetic patients. Especially is this true of block anesthesia, for its use does not injure the operative site itself. It is inadvisable to employ procaine by local infiltration in a region which has a deficient circulation, on account of the danger of producing gangrene or infection.[22, 23] Dewes contended that the slight hyperglycemia which follows the use of local anesthesia (for extraperitoneal operations) is due to the anesthetic agent. He said that the hyperglycemia is much greater in cases in which laparotomies are performed than it is in cases in which other operations are performed; in the former cases the value for the blood sugar sometimes is two to four times the normal figure. Lynn noted that the increase in the value for the blood sugar was 30 to 60 mg. per 100 c.c. following block anesthesia; this probably was attributable, at least in part, to a fall (about ten points) in the blood pressure.

Spinal anesthesia is generally conceded to be very useful for diabetic patients. Hailes contended, and with justification, that it should not be used in cases in which the patients were debilitated as such patients cannot tolerate a decrease in blood pressure, but diabetes itself is no contraindication to the use of spinal anesthesia. Vogel reported excellent results from the use of spinal anesthesia for amputation of the lower extremities of diabetic patients.

Preoperative and postoperative care of the diabetic patient is of great importance. Eliason recommended determination of blood sugar and carbon dioxide combining power of the plasma before operation. If the value for the carbon dioxide combining power is found to be low, he said that operation should be postponed until the acidosis has been overcome, for although the patient might survive the operation he might succumb to postoperative acidosis. Eliason also favored routine determinations of the values for the blood sugar and the carbon dioxide combining power of the plasma within five hours after operation.

Joslin advised the use of a small dose of morphine in order to avoid too great a respiratory depression, and McKittrick and Pratt did not use any opiate before operation, as opiates cause hyperglycemia. Le-

mann recommended the use of an extra carbohydrate feeding with an appropriate dose of insulin six to eight hours before the operation, and 20 c.c. of 50 per cent solution of dextrose with one or two units of insulin per gram of dextrose during the administration of the anesthetic. Intravenous administration of dextrose and insulin has not been used during operations at the clinic.

Chloroform is an especially dangerous anesthetic for diabetic patients and should not be used. Administration of ether to diabetic patients causes hyperglycemia, a concentration of blood fats, a suppression of renal function, and a pronounced tendency to acidosis. In spite of these obvious disadvantages it may be administered when its use shortens the operating time and facilitates the work of the surgeon, provided that the amount used is small.

Nitrous oxide and ethylene have only a slight tendency to cause acidosis and are satisfactory anesthetic agents for diabetic patients. It is essential that anoxemia be avoided. Procaine used as a local anesthetic is very valuable, especially when employed for block anesthesia. Local infiltration should be avoided in regions which are infected or which have an impaired circulation. Spinal anesthesia is useful for many operations on diabetic patients and has no contraindication peculiar to the disease.

Two hundred forty-four cases in which diabetic patients were operated on at the clinic from January 1, 1932, to January 1, 1934, were studied.[29] Of these patients, 108 were males and 136 were females. The youngest was six years of age and the oldest was eighty-two years.

Diabetes was graded on the basis of the severity of the disease;[1] thus, grade 1 includes those cases in which simple dietary regulation suffices to control the disease; grade 2 includes cases in which insulin is not required but strict and accurate regulation of the diet is necessary; grade 3 includes those cases in which the patients required 30 units or less of insulin and tolerated between 70 and 140 gm. of carbohydrates; grade 4 includes those cases in which more than 30 units of insulin are required in addition to a careful regulation of the diet.

Two hundred seventy-nine operations were performed on the 244 patients in this series. Tables were compiled to show the incidence of various complications and death in diabetes following anesthesia. In Table I the different anesthetic agents are listed with the number of times each was used in this series. Table II shows the ages of the patients and Table III shows the cases grouped according to the site of operation.

## SUMMARY AND CONCLUSIONS

Among the complications three groups are of interest. In 5 cases the grade of the diabetes was increased, as shown by the need for additional insulin. In 2 of these cases this change was permanent, while in the third case it was only a temporary aggravation. In 9 cases infection

TABLE I

MORTALITY AND INCIDENCE OF COMPLICATIONS FOLLOWING THE ADMINISTRATION OF VARIOUS ANESTHETICS IN OPERATIONS ON DIABETIC PATIENTS

| ANESTHETIC | ANESTHESIAS | INCREASE IN SEVERITY OF DIABETES | | COMPLICATIONS | | | | | | | | | | DEATHS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | RESPIRATORY | | CIRCULATORY | | GENITO-URINARY | | INFECTIONS | | MISCELLANEOUS | | | |
| | | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| Ether (1 to 4 oz.) with or without other agents | 48 | 1 | 2.1 | 1 | 2.1 | | | 2 | 4.2 | 1 | 2.1 | | | 4 | 8.3 |
| Ether (4 to 8 oz.) with or without other agents | 24 | | | 2 | 8.3 | 2 | 8.3 | | | | | 1 | 4.2 | 1 | 4.2 |
| Ether with or without other agents, including less than 1 oz. of ether | 76 | 3 | 3.9 | 2 | 2.6 | 1 | 1.3 | | | 1 | 1.3 | 3 | 3.9 | 7 | 9.2 |
| Local or regional anesthetics used alone | 33 | | | 1 | 3.0 | | | | | 1 | 3.0 | 1 | 3.0 | 2 | 6.1 |
| Spinal anesthetic with or without gas | 56 | 1 | 1.8 | 3 | 5.3 | 2 | 3.6 | 2 | 3.6 | 3 | 5.3 | | | 1 | 1.8 |
| Cocaine | 19 | | | | | | | 1 | 5.3 | | | | | | |
| Tribromethanol (avertin) | 1 | | | | | | | | | | | 1 | 100.0 | | |

TABLE II

MORTALITY AND INCIDENCE OF COMPLICATIONS ACCORDING TO AGE OF PATIENTS

| AGE OF PATIENTS, YEARS | PATIENTS | INCREASE IN SEVERITY OF DIABETES | | COMPLICATIONS | | | | | | | | | | DEATHS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | RESPIRATORY | | CIRCULATORY | | GENITOURINARY | | INFECTIONS | | MISCELLANEOUS | | | |
| | | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| 0-10 | 5 | | | | | | | | | | | | | | |
| 10-20 | 4 | 1 | 25.0 | | | | | | | | | | | | |
| 20-30 | 8 | | | | | | | | | | | | | | |
| 30-40 | 27 | | | 2 | 7.4 | 1 | 3.7 | | | | | 2 | 7.4 | | |
| 40-50 | 41 | 1 | 2.4 | 3 | 7.3 | | | 2 | 4.9 | 2 | 4.9 | 1 | 2.4 | 2 | 4.9 |
| 50-60 | 60 | | | 3 | 5.0 | 1 | 1.7 | 1 | 1.7 | 2 | 3.3 | | | 4 | 6.6 |
| 60-70 | 79 | 3 | 3.8 | | | 3 | 3.8 | | | 2 | 2.5 | 3 | 3.8 | 8 | 10.1 |
| 70-80 | 18 | | | 1 | 5.5 | | | 2 | 11.1 | | | | | 1 | 5.5 |
| 80-90 | 1 | | | | | | | | | | | | | | |
| Not recorded | 1 | | | | | | | | | | | | | | |

TABLE III

MORTALITY AND INCIDENCE OF COMPLICATIONS ACCORDING TO SITE OF OPERATION

| SITE OF OPERATION | OPERATIONS | INCREASE IN SEVERITY OF DIABETES | | COMPLICATIONS | | | | | | | | | | DEATHS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | RESPIRATORY | | CIRCULATORY | | GENITO-URINARY | | INFECTIONS | | MISCELLANEOUS | | | |
| | | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| Lower extremities | 16 | | | | | 1 | 6.3 | | | | | | | 3 | 18.8 |
| Perineum (including punch operation)* | 58 | | | | | 1 | 1.7 | 2 | 3.4 | 1 | 1.7 | | | 1 | 1.7 |
| Abdomen | 83 | 1 | 1.2 | 6 | 7.2 | | | 2 | 2.4 | 3 | 3.6 | 3 | 3.6 | 5 | 6.0 |
| Thorax and breast | 13 | 2 | 15.4 | | | 1 | 7.7 | | | | | | | 1 | 7.7 |
| Upper extremities | 8 | | | | | | | | | | | | | 1 | 12.5 |
| Neck | 58 | 2 | 3.4 | 3 | 5.5 | 1 | 1.7 | | | 1 | 1.7 | 1 | 1.7 | 4 | 6.9 |
| Head | 43 | | | | | 1 | 2.3 | 1 | 2.3 | 1 | 2.3 | 2 | 4.6 | | |

*Transurethral prostatic resection.

followed the operation. Three of these cases are included under the heading "Genitourinary Complications" in the table. In 2 other cases there was delayed healing. In these last 2 cases the complications included conditions which often are encountered in cases of diabetes and which should not be attributed to the anesthesia except as the latter may have caused a transitory increase in the severity of the diabetes. The other complications encountered are those seen on any surgical service.

Of the 15 deaths in this series, the earliest occurred on the third postoperative day and the others occurred at longer intervals up to twenty-two days. It is difficult to blame an anesthetic for a death that occurs many days after the use of the anesthetic. It is interesting that in many of the postoperative notes in this group of cases mention was made of the fact that the diabetes was under reasonably good control. Nearly all the anesthetics in common use were employed in one or more of these fatal cases, but cyclopropane, tribromethanol (avertin), or cocaine were not used. The largest quantity of ether used was 7 ounces (210 c.c.), the next largest amount was 2 ounces (60 c.c.), and 1 ounce (30 c.c.) or less was used in the other cases; therefore, ether did not play a conspicuous part in a large percentage of these fatalities. The duration of operation and anesthesia in this group of cases averaged about sixty-three minutes, which is at least suggestive.

From these data we may be justified in concluding that the usual anesthetic agents may be used for a diabetic patient provided the diabetes is carefully controlled preoperatively and postoperatively. This is true provided that reasonable care is taken to avoid surgical procedures which are of unusually long duration and provided that the anesthetic is administered with reasonable skill, without the use of excessive amounts of ether. In Table I it may be noted that the mortality was least following the use of spinal anesthesia. Table II demonstrates that the danger of a fatal outcome following operation increases in direct proportion to the age of the patient. Thus, the mortality encountered in cases in which patients were below the fifth decade of life (44 patients) was 0; in the fifth decade it was 4.9 per cent, and in the seventh decade it was 10.1 per cent. In Table III one may be surprised to note that the mortality was highest for patients who underwent surgical procedures on the lower extremities. This, however, is readily explained. In the majority of these instances amputation was done for diabetic gangrene and infection. The risk was recognized, but it was deemed essential that the operation be undertaken. It appears that the risk of operation is greater for patients suffering from diabetes than it is for the average individual and that the danger encountered following surgical procedures varies directly with the grade of diabetes. We are not convinced, however,

that statistics obtained on a larger group of cases will bear this out. Studies of other series may reveal that our conclusions may be explained by inclusion, in this group, of cases of infected diabetic gangrene or of the other cases of diabetes complicated by infection, in which such operations as emergency procedures are performed.

It is recognized, however, that infection and gangrene are not infrequently an intimate part of the syndrome of diabetes and therefore we feel that our conclusions are not unwarranted.

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# ACUTE APPENDICITIS

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THIS paper is a critical review and examination of 1,325 consecutive operations on acutely inflamed appendices performed at Mt. Sinai Hospital, Cleveland, from January, 1924, to November, 1935. We wish to emphasize the point that they were all acutely inflamed as reported by the pathologist and no case diagnosed as catarrhal or subacute has been included. The patients were operated on by the visiting staff and by the courtesy staff and include both private and ward service cases.

There were 748 males and 577 females. Seven hundred and eleven cases were between the ages of ten and thirty years.

Table I

| AGE | MALE | FEMALE | TOTAL |
|---|---|---|---|
| Under 5 yr. | 18 | 7 | 25 |
| 5 to 9 yr. | 73 | 58 | 131 |
| 10 to 19 yr. | 205 | 183 | 388 |
| 20 to 29 yr. | 180 | 143 | 323 |
| 30 to 39 yr. | 149 | 85 | 234 |
| 40 to 49 yr. | 74 | 37 | 111 |
| 50 to 59 hr. | 26 | 34 | 60 |
| Over 60 yr. | 14 | 16 | 30 |
| Over 70 yr. | 6 | 1 | 7 |
| Age unstated | 3 | 13 | 16 |
| | 748 | 577 | 1,325 |

The high percentage of patients operated on within 24 hours of the onset of symptoms was a factor in the low mortality rate. There were 1,020 cases admitted within 48 hours after onset, and of these 738 came within 24 hours. The duration of symptoms varied from 6 hours to 1 month. Those patients who had symptoms less than 12 hours totaled 226; 1 day, 512; 2 days, 282; 3 days, 122; 4 days, 46; 5 days, 20; 6 days, 13; 7 days, 29; 8 days to 1 month, 35. Although many of these cases were operated on early; many already had ruptured appendices with peritonitis. It is apparent that quite some degree of inflammation must be present in the appendix hours before it begins to give symptoms. Therefore, keen diagnostic ability and cooperation of the internist and family physician make possible early surgical intervention in acute appendicitis.

Received for publication, May 26, 1937.

Pain was the predominating symptom. It occurred alone in 248 cases; with nausea in 198; with vomiting in 408; with nausea and vomiting in 460.

In addition to the above cardinal symptoms the following were noted:

TABLE II

| | |
|---|---|
| Chills | 59 |
| Diarrhea | 28 |
| Constipation | 15 |
| Dysuria | 15 |
| Urinary frequency | 4 |
| Backache | 9 |
| Sore throat | 9 |
| Nasopharyngitis | 13 |
| Fainting | 2 |
| Cold sweats | 2 |
| Malaise | 5 |
| Auricular fibrillation | 1 |
| Headache | 24 |
| Cases unstated | 11 |

The white blood count, although not all important, should not be overlooked. It ranged from a low of 2,300 to a high of 46,000 in our series. If one considers a leucocytosis as beginning with 10,000, then a count is of little value as a diagnostic aid in 12 per cent of the cases. This is sufficient evidence to prove that the clinical history and physical findings are much more important and valuable in arriving at a diagnosis. We are all too familiar with the number of cases of gangrenous appendicitis with a low white blood count to permit the latter to deter us from operation. On the other hand, a very high white blood count with minimal physical findings may be accepted as an aid to diagnosis and an additional indication for operation.

TABLE III

| W.B.C. | NO. |
|---|---|
| Below 5,000 | 4 |
| 5,000 to 7,900 | 37 |
| 8,000 to 9,900 | 104 |
| 10,000 to 11,900 | 126 |
| 12,000 to 14,900 | 319 |
| 15,000 to 19,900 | 376 |
| 20,000 to 24,900 | 148 |
| 25,000 to 29,000 | 39 |
| Over 30,000 | 25 |

The cases with free purulent fluid or fibrin localized to the appendix bore a pathologic report of localized peritonitis and numbered 870. This report of the pathologist must not be taken too literally in considering the severity of these cases. In other words, it does not mean that there was no fibrin or peritonitis in the rest of the abdominal cavity. On the contrary, it means there probably was peritonitis elsewhere and more widespread, but the pathologist had only the appendix to examine;

whereas, the surgeon could and should have noted how severe the reactions were elsewhere. The report of localized peritonitis is only an index of what undoubtedly was more widespread and shows that the infection and reaction were no longer confined within the walls of the appendix. The mortality in this group was 5 per cent. For the whole series there were 57 deaths, or 4.3 per cent, and among these 57 deaths there were 7 cases in which the appendix was not removed or seen. There were 187 cases of ruptured appendices, 14.1 per cent of the series. Twenty-one of these died, a mortality of 11.2 per cent for ruptured appendicitis.

DeCourcy reports the mortality rates for ruptured appendicitis from the Good Samaritan Hospital yearly from 1931 to 1935 varied from 24.5 per cent to 11.4 per cent, although he states that in a series of 50 cases he has reduced the mortality of ruptured appendicitis to 4 per cent by inserting a tube in the cecum after removing the appendix. He believes that decompression of the bowel is a very important factor in saving life in the case of ruptured appendicitis and his figures show that it should be given serious consideration. However, as again stated under the question of drainage, in our series 77 of the ruptured appendicitis cases were closed without drainage with a mortality of 4 cases, or 5.3 per cent; whereas, the mortality in the 110 cases of ruptured appendices that were drained was 15.4 per cent.

We found that a fecalith played an important rôle in the mortality figures. It was present in 184 appendices, or 14 per cent of the series, and was also in evidence in 18 of the 50 fatal cases, or 36 per cent of the total deaths. In other words, the 184 appendectomies where a fecalith was noted had a mortality of 9.8 per cent; whereas, the rest of the 1,141 appendectomies free from fecaliths carried a mortality of only 39, or 3.4 per cent. Thus the mortality in the presence of a fecalith was 3 times as high as in the absence of a fecalith. It was noted in all age groups, the youngest being three years of age and the oldest over sixty years. It appeared in 117 males and 67 females. They were operated on just as early as those cases in the general group. Seventy-eight (42 per cent) of these patients were admitted with symptoms of 1 day's duration; 58 (31 per cent), 2 days' duration. These percentages are almost the same as in the general group so that delay and age were not factors in the mortality figures.

In considering the pathologic conditions present in this group, we are struck with the severity of the disease process as reported by the pathologic laboratories. There were only 15 cases in this group admitted within 12 hours of the onset, as against 226 in the general group—a relative percentage of 8.1 per cent as against 17 per cent—yet 12 of these 15 early cases showed regional fibrinopurulent peritonitis. There was a total of 138 cases of this group of 184 which had regional fibrinopurulent peritonitis. Thus we can say that the infection spread more rapidly

beyond the walls of the appendix. There were 41 ruptured appendices in the 184 cases with fecaliths—22.3 per cent, as against 146 ruptured appendices in 1,141 cases—12.7 per cent. It is possible that the fecalith is responsible for a more rapid progress of the disease by tending to promote earlier rupture or earlier gangrene because of obstruction and resulting distention; consequently it is directly responsible for a great many deaths. Since this was written, Wangensteen and Bowers have published their results of experiments with obstructed appendices. Their results seem to agree with our clinical observations in this series of fecaliths.

Wilkie has pointed out that there are two primary and fundamental processes occurring in appendicitis. One is the acute infection of the wall of the appendix, the other an acute obstruction of the lumen of the appendix comparable to any other obstruction of the bowel. Kline stresses infection in false, microscopic diverticulae. Wilkie states in this type the rise of temperature is natural and inevitable. But in the obstructive type, this rise is absent during the early phase, at the very time when diagnosis is all important. While Wilkie does not believe that obstruction precedes infection in all cases, he does believe that blocking of the lumen, with consequent tension, is the real danger in appendicitis. It is unfortunate that the fecalith does not produce earlier symptomatology. In other words, this further brings out the fact well noted by many writers that symptoms and physical findings may be disproportionate to the pathologic condition present in acute appendicitis.

We examined our figures to note carefully the effects of drainage on mortality, morbidity, and complications. We have a sole positive indication for drainage, the localized walled-off abscess. It has been well established that a drain in the abdomen does not drain the abdomen for long, but that it becomes walled off in 14 to 20 hours or less and thereafter acts as a plug and a foreign body, thereby taxing the body economy. Nevertheless, a good many surgeons still drain the abdomen on the slightest provocation—so great is habit and the effect of past tradition. We consider first the 187 ruptured appendices with 21 deaths. Of these 187 cases, 110 were drained intraabdominally. Twenty-five were drained subfascially. There were 52 cases not drained at all, but these latter two groups may be added together totaling 77 cases in which the abdomen was actually not drained. There were 16 deaths in the group in which the abdomen was drained, a mortality rate of 16/110 or 14.5 per cent. There were 4 deaths in the group of cases with undrained abdomens, a mortality rate of 5.3 per cent. We believe these figures are important in emphasizing the dangers of drainage.

There were 31 cases operated upon in which drainage was the only procedure. There were 6 deaths (19.3 per cent). The average duration of symptoms was 7.9 days. The shortest duration of symptoms was 12

hours in a six-year-old girl and yet a walled-off abscess was found at operation. Sometimes drains were inserted when there was no walled-off abscess. They were all cases, however, in which the surgeon found pus and in which he thought it was better not to look for the appendix or to attempt to remove it. This group of cases is highly instructive and is worth while analyzing more in detail. There were 16 females and 15 males. The youngest was a sixteen-month-old boy. The oldest, a female, definitely well over sixty years of age. Interesting enough, there were 16 cases under fifteen years of age, among whom there were only 2 deaths.

TABLE IV

| DURATION OF SYMPTOMS | NO. |
|---|---|
| 12 hr. | 1 |
| 2 days | 2 |
| 3 days | 4 |
| 4 days | 3 |
| 5 days | 2 |
| 6 days | 3 |
| 7 days | 3 |
| 9 days | 2 |
| 10 days | 5 |
| 12 days | 1 |
| 14 days | 2 |
| 3 wk. | 1 |
| Unstated | 2 |

By far, the greater number of cases were of more than 4 days' duration. There were 744 hospital days for 31 cases, for an average of 24 days per case. There were 26 abscesses; the rest had general peritonitis. Fourteen were drained properly by opening into the abscess and not penetrating the general abdominal cavity.

The six deaths in this group are interesting to analyze in detail:

CASE 1.—(N 2215) A white boy, aged eleven years, who had been ill six days before admission to hospital. An appendiceal abscess was drained through the rectum. The boy developed intestinal obstruction and peritonitis. An ileostomy was done, then an incision and drainage for abscess of the left side of the abdomen. He was given blood transfusions but nevertheless died on the forty-ninth hospital day. In retrospect, there is nothing that could have been done to save this boy except perhaps an earlier visit to the doctor.

CASE 2.—(N 230) A white woman, aged forty-six years, who had been ill ten days. She was explored for gallbladder disease. An appendiceal abscess was found which was inadvertently ruptured with a spill of pus into the general abdominal cavity. Peritonitis developed. The patient died in five days.

CASE 3.—(108-1225) A white male, aged forty years, who was ill three days. The patient had a diffuse peritonitis. He was also a diabetic. No attempt was made to locate the appendix. He had a massive intestinal hemorrhage on the eighth day, which at autopsy was found to have come from a gastric ulcer.

CASE 4.—(108-201) A nine-year-old girl, ill two days. The doctor decided upon a waiting policy. She was operated upon on the ninth day when her temperature, which had been coming down, suddenly began to rise. An appendiceal abscess was

opened through the free peritoneal cavity and was drained. She developed a fecal fistula and then a massive hemorrhage from the abdominal incision. She was transfused with whole blood several times. She died on the twenty-ninth day. This case does not militate against conservative treatment or against drainage only of an abscess. The case brings up the question of the proper method of draining an appendiceal abscess. It is always best if the abscess points toward the rectum or in the culdesac to drain through the rectum or vagina, respectively. However, when the abscess must be opened through the abdominal wall, great care must be taken to open the abscess laterally without opening the peritoneal cavity.

CASE 5.—(108-2784) A white male, sixty-eight years old, who had been ill three and one-half days, came into the hospital nearly moribund. At operation a large amount of free fluid was found and considerable pus. The appendix was retrocecal and gangrenous. No effort was made to remove it. The patient died in eight hours.

CASE 6.—(108-344). A fifty-nine-year-old woman, ill ten days. A diabetic in very poor condition. The patient had peritonitis plus a large abscess in the right iliac fossa which was ruptured accidentally, liberating a large quantity of very foul pus. The patient lived two days.

Thus, of the 6 deaths, 4 were apparently inevitable because of the patient's condition or the state of the disease on admission. Two patients might have been saved with different technique. The deaths in this group were due to peritonitis, intestinal obstruction, toxemia, massive hemorrhage (a) from abdominal wound, (b) from intestines—from gastric ulcer, paralytic ileus.

We next consider the effect of drainage on morbidity. There were 8,484 hospital days in the nondrained group. An average of 10.7 days. There were 69 cases in which a subfascial drain was used, but in which the abdominal cavity was not drained, that spent a total of 1,079 days in the hospital, for an average of 15.3 days. The closeness of this figure with that of 15.6 days in cases in which an abdominal drain was used would seem to indicate that the delayed healing of the abdominal wall was the only factor in prolonging their hospitalization.

The complications which arose in this group were general peritonitis, intestinal obstruction, decubitus ulcers, pelvic abscess, parotitis, submaxillary abscess, fecal fistula, massive hemorrhage from abdomen, massive intestinal hemorrhage, pleural effusion, subphrenic abscess, bronchial pneumonia, paralytic ileus, right lumbar abscess.

Of the 57 deaths, 38 patients were drained—approximately 65 per cent of the cases that died. Of course, it may be granted that these were mostly severe cases and included in these 38 deaths were 7 in which the appendix was not removed. There were 462 cases in which the abdomen was drained. The mortality rate for these is 8.03 per cent. In the nondrained group, the mortality is 2.21 per cent. Included in the series of 462 drainage cases are many cases which occurred in the earlier years of this study and doubtless would not be drained today.

The following is a consideration of the complications:

1. Wound infection: We may consider every drained case a wound infection. There were 128 wound infections in the 794 nondrained cases, 16.18 per cent.

2. Pelvic abscess: Pelvic abscess is a common complication in appendicitis. There were 33 pelvic abscesses developed in the drained cases, 7 per cent. There were 11 pelvic abscesses in the subfascial drained group and 10 in the undrained group. These latter two groups may be added together for a total of 21 pelvic abscesses in 862 cases, 2.4 per cent. Therefore, pelvic abscess occurs over 3 times more frequently when the abdomen is drained.

Some attempt was made to correlate the amount of fluid present in the abdomen with the development of a pelvic abscess. Naturally this must be crude inasmuch as the actual amount of fluid present is never measured. Whether there is a large or small amount of fluid present is never measured. Whether there is a large or small amount of fluid noted on the chart differs with the temperament of the observer. Nevertheless, we thought it worth while to see what we could find.

TABLE V

| | ABDOMEN NOT DRAINED | PELVIC ABSCESS FOLLOWED | SUB-FASCIAL DRAIN | PELVIC ABSCESS FOLLOWED | ABDOMEN DRAINED | PELVIC ABSCESS FOLLOWED |
|---|---|---|---|---|---|---|
| No free fluid | 373 | | 25 | | 219 | |
| Small amount free fluid | 334 | 5 | 26 | 1 | 191 | 13 |
| Large amount free fluid | 76 | 5 | 16 | 10 | 61 | 20 |
| Unstated | 11 | | 2 | | 1 | |

We may group the cases where the abdomen was not drained and where it was subfascially drained together and we may also add the cases of no free fluid and the cases with a small amount of fluid together. Accordingly, we find that in the drained abdomens group where there was a large amount of fluid present, 20 out of 61, or nearly 30 per cent, developed a pelvic abscess. In the combined undrained groups, when there was a large amount of fluid present, only 15 out of 92 developed a pelvic abscess, 16.3 per cent. We may accordingly surmise that when there is a large amount of fluid present, a pelvic abscess may be a common complication regardless of whether the abdomen is drained or not, but nevertheless it is twice as frequent when the abdomen is drained. When there was a small amount of fluid present and the abdomen was drained, 13 out of 400, or 3.3 per cent, developed a pelvic abscess; but when the abdomen was not drained, only 6 out of 758, or 0.8 per cent, developed a pelvic abscess. Thus, drainage as a causative factor in the formation of a pelvic abscess is still more evident in this group of cases.

Fecal fistula occurred 16 times in the 462 drained cases—3.4 per cent. There was 1 fecal fistula in the subfascial drain group and 4 in the

nondrainage group—a total of 5, or 0.5 per cent. Therefore, fecal fistula may be expected 7 times more frequently when the abdomen is drained. There were 2 cases of bad dehiscence of the wound in the drained group. There was none in the other groups.

We list the more common complications in Table VI.

TABLE VI

| | ABDOMEN DRAINED | ABDOMEN NOT DRAINED | SUBFASCIAL DRAIN |
|---|---|---|---|
| Pelvic abscess | 33 | 10 | 11 |
| Wound infection | 100% | 128 | 100% |
| Fecal fistula | 16 | 4 | 1 |
| Intestinal obstruction | 4 | 2 | 0 |
| Paralytic ileus | 5 | 3 | 1 |
| General peritonitis | 5 | 11 | |
| Lobar pneumonia | 10 | 6 | |
| Bronchopneumonia | 15 | 8 | |
| Embolic deaths | 2 | 0 | |

Altogether there were, exclusive of wound infections, 139 complications in the drained cases—30 per cent, there were 108 cases with complications exclusive of wound infections in the undrained group—12.5 per cent—less than half as common as in the drained group. In the whole series there were, exclusive of wound infections, which you must remember is of very high incidence, 247 complications, or 18.7 per cent. In other words, the appendectomy is often the easiest part of the procedure in the cases of appendicitis. The early recognition and proper treatment of the complications arising from acute appendicitis tax the ingenuity and ability and wisdom of every surgeon. One out of every 3 cases of appendicitis operated upon has some complication arising. Here is a great field in which to recognize and to treat properly each complication to cut down the mortality. It is easy to see now why operations are always so successful, and yet so many people die of complications. The surgeon who drains an abdomen in acute appendicitis immediately doubles the risk of a complication, aside from trouble with the wound which is nearly always present in some degree. Rather than increasing the life expectancy of the patient, he definitely lowers it.

### ANALYSIS OF CASES THAT DIED

Of the 57 deaths, 33 were male and 24 female. The youngest was a six-month-old white girl. The oldest stated age was seventy-four years, a white woman. There were 19 patients under fifteen years of age. There were 14 over fifty years and 8 of these over sixty years—a total of 33 in the extremes of life. The duration of the symptoms was up to 1 day, 9 cases; up to 2 days, 12 cases; 2 to 3 days, 17 cases; 3 to 4 days, 4 cases; 4 to 5 days, 2 cases; 5 to 6 days, 3 cases; 6 to 7 days, 6 cases; 10 days, 2 cases; unstated, 2 cases. By far most of the cases had symptoms over 36 hours. Thirty-six cases had symptoms over

48 hours, 62.3 per cent of the deaths. Four cases had had chills. There were 59 cases in our entire series who complained of chills. Chills, therefore, should not be looked upon as indicating a poor prognosis. Two cases had cough, 1 hiccoughs. Two cases were not operated upon. Six cases were operated upon and drained only. Thirty-seven cases were drained through the abdomen. One case was drained through the rectum. Fecalith was found and mentioned in 18 cases in which the appendix was removed. The 57 cases had a total of 599 hospital days, for an average 10.5 hospital days, but 18 of these cases lived but 2 days or less after admission which indicates a very virulent infection or that they were ill a long time and in poor condition and the operation hastened their end. Twenty-one cases, nearly 37 per cent, gave histories of having had cathartics and several more had had enemas.

Most writers find great difficulty in drawing the dividing line between the localized and the spreading types of peritonitis. We believe it is altogether too difficult and too hazardous to try to determine this at operation. Certainly if a McBurney incision is used, the view of the abdomen is quite limited. Most surgeons use this type of incision. The important factors in any infection are the virulence or numbers of the infecting organisms and the resistance of the patient. It seems to us that more and better information is given if the presence or absence of pus or cloudy fluid and the amount present are stated rather than to attempt to guess what type of peritonitis it is. Accordingly, we find in this group of 57 deaths that 27 had large amounts of free pus or cloudy fluid. Ten had small amounts. There were 10 cases with no fluid and 8 cases with walled-off abscess. There were 2 cases not operated upon. A large amount of free pus or cloudy fluid more readily represents a spreading type of peritonitis, especially when there is no walling off, although even this is not always the case. Accordingly, there were cases in which no fluid was present which later died of generalized peritonitis.

In this group of 57 fatal cases, the leucocyte count ranged from 2,360 in a seventy-four-year-old woman who had been ill 2 days, to 42,000 in a twelve-year-old girl, ill 7 days. (There were 9 white counts of 10,000 or less in 55 done.) Most cases were operated upon soon after admission under nitrous oxide oxygen ether. An occasional case was done under spinal anesthesia. There were many complications among these cases. The major complications were peritonitis, paralytic (adynemic) ileus, intestinal obstruction (dynamic), uremia, bronchopneumonia, lobar pneumonia, pelvic abscess, abdominal abscess, pylephlebitis, septicemia, suppurative parotitis, gas bacillus infection, empyema, subphrenic abscess, embolism, fecal fistula, psychosis (attempt at suicide), hemorrhage from abdominal wound, massive intestinal hemorrhage, circulatory collapse, shock, cellulitis of wound, cardiac failure, phlebitis, bed sore, disruption of wound, lung abscess, gangrene of scrotum. We

find peritonitis in 20 cases; paralytic ileus, 9 cases; pneumonia and bronchopneumonia, 11; unstated type, 5; pelvic abscess, 6; suppurative parotitis, 4; fecal fistula, 2. Peritonitis, pneumonia, paralytic ileus, and intestinal obstruction were the chief causes of death along with the toxemia that is present in the tremendous infection of the peritoneal cavity.

We believe surgery alone has reached its limit in combating acute appendicitis. Our hope for greater success lies in two directions. Cases must be brought to operation earlier. This problem can be solved by continued education, both of the people at large and of the doctor in general practice. A diagnosis of acute appendicitis in the very early stages is extremely difficult at times, but it is a life saver. We must continue to publicize the dangers resulting from the careless use of cathartics. However, one cannot hospitalize every stomachache. We cannot insist on the removal of every appendix because the total number of people dying from prophylactic appendectomy would easily be greater than the number dying now from acute appendicitis. The chief cause of death in appendicitis is peritonitis and the toxemia arising therefrom and from intestinal obstruction. Early operations will usually prevent these.

## CONCLUSIONS

1. We have studied 1,325 consecutive cases of acute appendicitis operated upon at Mt. Sinai Hospital from January, 1924, to November, 1935, with a mortality of 4.3 per cent.

2. We feel that the fecalith is directly responsible for a greater virulence of an attack by tending to produce earlier and greater pathologic change although it produced no earlier symptomatology.

3. The mortality is definitely greater in the presence of fecaliths.

4. We have shown that complications occur much more commonly when the abdomen is drained. Of the commonest complications, pelvic abscess is 2 to 4 times as frequent and fecal fistula is 7 times as frequent.

5. When the abdomen is drained, the morbidity is prolonged and mortality is increased.

6. We feel that drainage of the abdomen in acute appendicitis should be sharply restricted to use in localized walled-off abscess.

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# BONE METASTASES FROM CARCINOMA OF THE STOMACH*

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CARCINOMA of the stomach is the most common cancer of the human body. Metastasis to the surrounding lymph nodes, the liver, and neighboring organs is very frequent and metastasis to the lungs is by no means uncommon. Metastasis to bone, however, is apparently rare and seldom have reports of its occurrence appeared in the literature. Moore,[1] in a study of 1,600 cases of carcinoma of the stomach, found no evidence of bone involvement. Jenkinson[2] found no tumors of the stomach in his series of gastrointestinal malignancies giving rise to bone metastases. In a series of 537 cases of carcinomas of the stomach from Johns Hopkins Hospital, Copeland[3] reports 7 cases with osseous lesions. Southerland[4] states that 1.9 per cent of his 1,032 cases of malignant bony metastases arose from primary growths in the stomach. A higher incidence of 2.5 per cent is given by Matthews,[5] and 5.7 per cent by Warren[6] in their series. Recently, Kerr and Berger[7] reviewed the literature and found 143 cases. To these they added 5 cases, making a total of 148 reported cases.

In a period of fifteen years, from January 1, 1920, to December 31, 1935, 606 patients were admitted to the Presbyterian Hospital upon whom a diagnosis of carcinoma of the stomach was made. Of this group, 10 gave symptoms of bone pains which might be attributable to bone metastases. Roentgenograms were made of the bony structures of these 10 patients and in not a single instance did the x-ray films show any evidence of osseous implants. Autopsies were obtained upon 7 of these 10 patients. In 3 of them metastatic lesions of the bones were found.

## REPORT OF CASES

CASE 1.—Mr. J. F., a carpenter, aged forty-five years, entered the Presbyterian Hospital May 8, 1933, complaining of upper abdominal pain, increasing weakness, and weight loss of twenty pounds during the past four months. Symptoms had been initiated with what he termed a "cold in the stomach" eighteen months previously, followed by increasing periods of epigastric pain and pressure, chiefly after evening meals. Soda had given little relief and induced vomiting had been resorted to with complete relief. Past history was of no importance.

*Examination.*—The patient was a pale, emaciated male whose tongue and skin were dry. His pupils reacted well to light and accommodation. The thyroid gland was of normal size and the cervical lymph glands were not enlarged. Heart and lungs were normal. The blood pressure was 96/68. The abdomen was scaphoid and no peristaltic waves were visible. A firm, fixed, slightly tender mass about 3.5

*Read before the Chicago Surgical Society, February 5, 1937.
Received for publication, July 7, 1937.

cm. in diameter was palpable in the epigastrium. The entire abdomen was soft and no tenderness or abnormal findings were elicited elsewhere. Rectal examination was negative. Reflexes normal.

*Laboratory Findings.*—R.B.C., 3,410,000; W.B.C., 6,600; Hb., 76 per cent. Blood Wassermann and Kahn tests negative. Ewald test meal: total acid, 86; free HCl, 24. Urine normal. Repeated stools showed strongly positive benzidene tests with absence of macroscopic blood. Roentgenograms of the stomach revealed a large filling defect of the antrum extending from the pylorus to well above the angularis.

*Operative Findings.*—At operation, a large carcinoma of the stomach involving the entire pyloric region was found. An extensive resection of the pyloric portion of the stomach and regional lymph nodes was done. No evidence of gross carcinoma remained. Postoperative recovery was uneventful and the patient left the hospital in two weeks.

December 23, 1933, seven months after operation, the patient reentered the hospital because of severe back pain. He had been improving generally until October, 1933, when an attack of dull backache incapacitated him for four days. Following this he had been symptom free until at the onset of an acute cold ten days previously he began to have unbearable back pains. Findings at examination were essentially the same as before except for the following: marked redness of the throat with bilateral cervical lymphadenitis; slight dullness over the left upper chest with few inconstant moist râles; abdomen soft with no palpable masses; marked tenderness, stiffness, and pain on motion of the entire spine. Temperature, 101° F. Pulse, 100. Roentgenograms of the spine showed a slight lipping of the dorsolumbar vertebrae, otherwise no evidence of bone change was seen. The patient rapidly became weaker and both lungs became involved in a terminal pneumonia.

*Autopsy Findings.*—Essential findings were as follows: Extensively resected stomach with freely functioning gastrojejunostomy; carcinomatous metastases of the gastrohepatic, periaortic, abdominal, periesophageal, tracheobronchial, anterior mediastinal, and lower cervical lymph nodes; neoplastic thrombosis of the portal vein; hemorrhagic bronchopneumonia; carcinomatous metastases of the liver and bodies of the dorsolumbar vertebrae and ribs.

CASE 2.—Mr. A. S., a milk-wagon driver, aged fifty-three years, entered Presbyterian Hospital April 19, 1933, complaining of epigastric pain, nausea, vomiting, and loss of weight. Four years previously he had experienced attacks of "indigestion" lasting a few days at a time which completely disappeared after about two months. Fifteen months prior to admission, a sudden return of his epigastric distress occurred and ulcer management was instituted elsewhere. From this he gained some relief, but the pain never completely disappeared. For three months previous to admission he had been having recurrent severe epigastric pain with nausea and vomiting. There was nothing of significance in his past history.

*Examination.*—The patient was anemic and dehydrated. Small bilateral shotlike enlargements of the posterior cervical lymph glands were palpable. The pupils were small and reacted to light and accommodation. The thyroid gland was not enlarged. Heart and lungs were normal. Blood pressure 110/70. Pulse 64. In the epigastrium a small slightly tender mass could be palpated. The liver, spleen, and left kidney were not palpable. The right kidney was normal. The rectum and prostate were normal. Reflexes normal.

*Laboratory Findings.*—R.B.C., 3,500,000; W.B.C., 7,200; Hb., 42 per cent. Blood Wassermann and Kahn tests negative. Ewald test meal: total acid, 88; free HCl, 9. Lactic acid bacilli were present in numbers. Urine normal. Stools were brown colored and contained marked chemical blood. Roentgenograms of the

stomach revealed a large filling defect extending from the pylorus along the lesser curvature to above the angle of the antrum.

*Operative Findings.*—At operation, an extensive carcinoma of the prepyloric portion of the stomach was found. The growth extended midway up the stomach. Regional lymph glands along the entire lesser curvature were involved. An extensive resection was done removing all the stomach to within a few centimeters of the esophagus. The patient made an uneventful recovery.

Nine months after operation the patient suddenly began a rapid loss of weight and developed pain in the back between the shoulders which extended down the spine and became quite severe. He was readmitted to the hospital February 3, 1934. On examination, the findings were essentially as before, except for marked tenderness over the dorsal and lumbar spine with considerable pain and limitation of motion. The abdomen was soft with no evidence of carcinomatous recurrence. Roentgenograms of the dorsal and lumbar spine showed no evidence of bone changes. The patient continued to lose weight rapidly, became weaker, and died of a pneumonia with carcinomatous metastases in both lungs.

*Autopsy Findings.*—These were essentially as follows: Resected distal end of the stomach with a freely patent gastrojejunostomy; carcinomatous metastases of the mesenteric and periaortic abdominal lymph nodes; carcinomatous metastases of the lungs and tracheobronchial lymph nodes; extensive carcinomatous metastases of the bodies of the dorsolumbar vertebrae, manubrium sterni, and ribs.

CASE 3.—Mr. A. E., an engineer, aged forty years, entered the Presbyterian Hospital September 11, 1935, complaining of epigastric distress, anorexia, and loss of weight for one year. Back pain had been present for five days. Accompanying the epigastric distress there had been nausea during the last two months and on several occasions vomiting had occurred. The back pain had been constant for five days and extended over the dorsal, lumbar, and sacral spine. He had been under the care of a doctor who, without x-rays or gastric analysis, had made a diagnosis of peptic ulcer and had treated the patient with alkaline powders and a milk diet. His symptoms had become progressively worse on this regime and the sudden back pain brought him into the hospital. His past history was of no importance.

*Examination.*—The patient had a marked pallor and apparently was having considerable pain. Pupils were small and reacted well to light and accommodation. There was moderate lymphadenopathy in both anterior triangles of the neck without tenderness. The thyroid gland was not enlarged. Heart and lungs were normal. Blood pressure, 120/76. Pulse, 100. The abdomen was soft. In the epigastrium there was moderate tenderness on deep palpation. No masses could be found. The liver and spleen were not palpable and the kidneys were of normal size and without tenderness. Reflexes were normal. Rectal examination revealed a soft prostate of moderate size with no tenderness. The spine was tender on percussion over the dorsolumbar region. Mobility was not limited on slow motion, although considerable pain was elicited. A neurological examination revealed no abnormal findings of the nervous system.

*Laboratory Findings.*—R.B.C., 2,940,000; W.B.C., 5,450; Hb., 47 per cent. Blood Wassermann and Kahn tests negative. Ewald test meal: total acid, 28; free HCl, 12. Urine normal. Repeated stool examinations showed no macroscopic but marked chemical evidence of blood. In roentgenograms of the stomach, a deformity of the lesser curvature could be seen, extending high on the posterior wall. Roentgenograms of the spine showed no evidence of bone change.

*Autopsy Findings.*—Essential findings were an ulcerative adenocarcinoma of the lesser curvature of the stomach with metastases to the perigastric, periaortic abdominal lymph nodes, and to the dorsolumbar spine.

DISCUSSION

To further confirm our negative findings in x-rays of the skeletal structures taken during the lives of these patients, we again x-rayed the bones in which gross metastatic lesions had been found at autopsy.

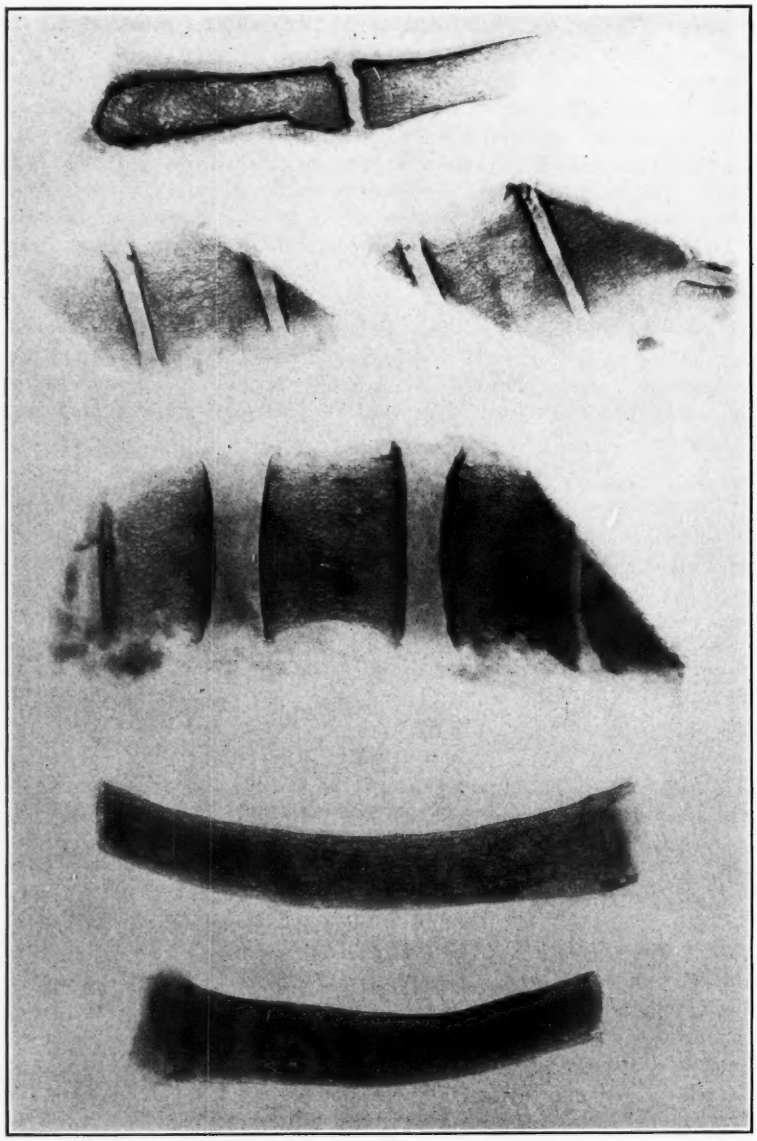

Fig. 1.—X-rays made after removal of bones, failing to show gross metastases.

With all obscuring shadows removed and a maximum of detail present, we were still unable to see any evidence of secondary growths in these x-rays (Fig. 1). Although metastasis to bone from primary carcinoma of the stomach is not common, it probably occurs more fre-

quently than is usually supposed. While secondary bony lesions may be suspected and searched for on the basis of clinical symptoms, if the roentgenograms fail to show the presence of gross lesions, as they have in our cases, many diagnoses must remain questionable or unconfirmed unless autopsy is permitted.

From the series of cases reported in the literature where the type of metastases has been noted, osteoplasia and osteoclasia have occurred in about equal numbers. Both types of change have been observed in the same individual. Few writers have expressed an opinion regarding the relation of the size, location, and type of the gastric lesion to the

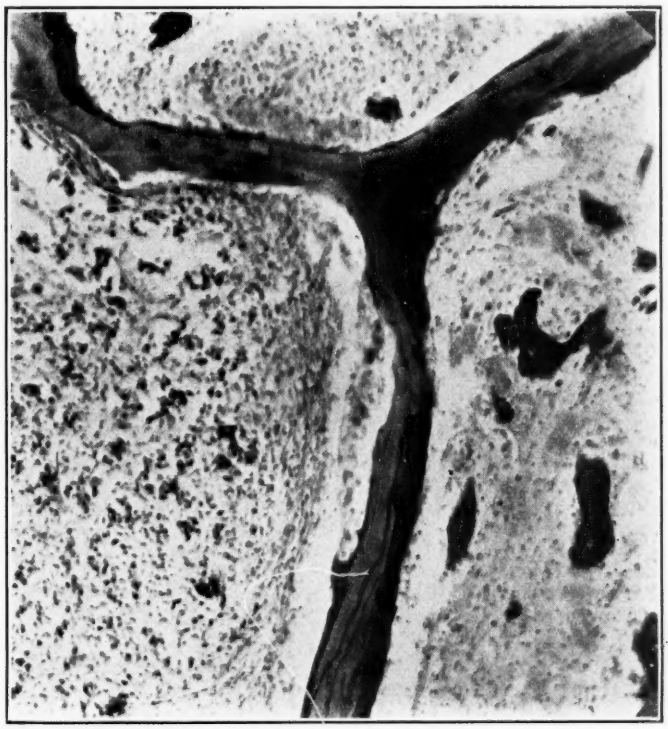

Fig. 2.—Microscopic section showing carcinomatous implants with absence of osteoplasia and osteoclasia.

osseous metastases. After a study of the recorded cases, Kerr and Berger are of the opinion that the size of the primary lesion, its site, and general type have no bearing on the probable occurrence of metastasis to bone. The primary growths in our three cases were extensive adenocarcinomas involving the prepyloric regions and a great part of the lesser curvatures. The metastatic growths to bone all gave the same gross and microscopic appearance. On cross-sections of the vertebrae were mosaic patterns of dark purple and opaque yellow-gray areas about equal in distribution. Microscopically, carcinomatous tissue was implanted between the trabeculations of the skeletal struc-

tures and very little osteoplasia or osteoclasia had taken place (Fig. 2). The fact that metastasis had taken place by filling the spaces of the bony meshwork without causing noticeable destruction or proliferation of bone is undoubtedly the reason for failure of the x-rays to reveal the presence of tumor growths.

## SUMMARY

1. Bony metastases from carcinoma of the stomach are rare, Kerr and Berger having been able to collect only 143 cases from the literature.

2. In a study of 606 cases of carcinoma of the stomach, 3 cases of proved bony metastases have been found.

3. Roentgenograms failed to show the presence of metastatic lesions in the 3 cases here reported, due to the absence of either osteoplastic or osteoclastic changes in the involved bones.

4. Bony metastases from carcinoma of the stomach may be more common than has been supposed. Diagnosis must depend entirely on clinical symptoms, where roentgenograms fail, and consequently cannot be confirmed in cases where necropsy is refused.

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# THE EFFECT OF CARBON ARC RADIATION ON WOUND HEALING

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THE influence of radiant energy on wound healing has been recently reviewed by Laurens[1] and Arey.[2] Many of the leading European heliotherapists, including Bernhard and Rollier, have extolled the merits of sunlight, both natural and artificial, and report marked benefit following its use, particularly in refractory wounds. Goldammer[3] found that the results were brilliant both in fresh and granulating wounds received in battle. Coulter and Smith[4] likewise think ultraviolet radiation of definite value in the treatment of wounds. Some workers,[5, 6] however, have found that healing is not hastened by artificial radiant energy. Coburn and Cowles[7] not only failed to find any benefit on treating a large series of rats by irradiation with carbon and iron arcs, but their work seemed to indicate a retarding effect. Pollaczek[8] found that doses slightly over optimal produced injurious effects.

Adult healthy dogs of medium size (5 to 8 kg.) with pink skin and white or light colored coats were used. The wounds were made in pairs, one on each side of the body in the saddle region and were as identical as possible, the left wound being the experimental while the right served as the control. The wounds were of two sizes, 18 and 40 mm. in diameter (255 and 1256 sq. mm.) and of skin depth. They were made with sharp cork borers placed firmly on the skin and rotated. This method prevents reflex contraction and results in round wounds with well-defined margins. Because of their position the wounds remained clean without bandaging and the animals could not lick them.

The wounds were measured at intervals throughout the healing period by placing a clean glass plate over them and tracing the periphery with a sharp pointed glass pencil, transferring this to paper and determining the area with a planimeter. Healing was considered complete when the scab fell off or could easily be brushed off leaving a dry cicatrix beneath.

Irradiation was begun one to three days following the operation. The animals were placed in a hammock so adjusted under their bodies as to allow them to stand or to rest in the supports during the irradiation. The conditions were varied in different groups by varying the duration of the exposure, the number of exposures per week, the dis-

Received for publication, July 22, 1937.

tance from the arc; by irradiating the whole left side of the animal or just the wound (local irradiation), by keeping some of the animals in complete darkness between irradiations, and by not irradiating some at all.

The source of radiant energy was a carbon arc lamp burning "sunshine" carbons, operated at between 24 and 27 amperes and with a potential drop across the arc of 50 to 60 volts. The total energy emitted was 0.475 gm. calories per square centimeter per minute at 1 M. distance, with a percentage distribution of ultraviolet 3, luminous 23.5, and infra-red 73.5.

## COMMENT

Table I summarizes the 29 small wound (255 sq. mm.) experiments. They can be divided into four groups. In the first three groups the whole side of the animal was irradiated with progressively increasing doses per group, while in the fourth group the exposure was limited to just the wound (local irradiation), the rest of the body being shielded from radiation. Since it seemed possible that the animals might be obtaining sufficient radiation between exposures to influence the healing time of the wounds, particularly the controls, these animals were also kept in complete darkness between treatments.

In 8 of the 29 experiments the irradiated wound healed more quickly and in 8 less quickly than the control, while in 13 there was no difference. In only one experiment (No. 18) was the acceleration in healing rate marked.

Since the results on the small wounds were indecisive, an attempt was made, in the second series, to obtain more definite results by using a larger wound (1,256 sq. mm.), thus prolonging the healing time and allowing the radiant energy more time to manifest its effects.

Table II summarizes all of the large wound experiments. Irradiation procedures similar to those for the small wounds of Table I were used. One group, however (Experiments 38 through 45), was given more frequent but shorter irradiations to more nearly simulate natural radiation. In 10 of the 19 large wound experiments, the irradiated wound healed more quickly and in 4 less quickly than the control, while in 5 there was no difference. In 2 experiments (Nos. 33 and 40) there was a marked and in 2 (Nos. 30 and 31) there was a moderate acceleration while in 1 (No. 32) there was a moderate retardation in the healing rate of the irradiated wound.

Table III summarizes 5 experiments with small wounds and 7 experiments with large wounds in which no carbon arc radiation was administered. Of the 5 small wound experiments, only 1 slight difference in healing time was noted. Of the 7 large wound experiments, 4 showed a difference in healing time, 3 of which were but slight while

TABLE I

SMALL WOUND EXPERIMENTS (LEFT WOUND IRRADIATED, RIGHT WOUND CONTROL)

| EXPERIMENT NUMBER | IRRADIATION PROCEDURE | TOTAL RADIANT ENERGY RECEIVED IN GM. CALORIES PER SQ. CM. | HEALING TIME IN DAYS | | DIFFERENCE |
|---|---|---|---|---|---|
| | | | LEFT | RIGHT | |
| 1 | Entire side for 10 minutes 3 times per week at 1 M. | 38.0 | 25 | 25 | 0 |
| 2 | Entire side for 10 minutes 3 times per week at 1 M. | 33.3 | 21 | 21 | 0 |
| 3 | Entire side for 10 minutes 3 times per week at 1 M. | 38.0 | 22 | 26 | +4 |
| 4 | Entire side for 10 minutes 3 times per week at 1 M. | 57.0 | 31 | 35 | +4 |
| 5 | Entire side for 10 minutes 3 times per week at 1 M. | 52.3 | 28 | 28 | 0 |
| 6 | Entire side for 10 minutes 3 times per week at 1 M. | 71.3 | 29 | 25 | -4 |
| 7 | Entire side for 15 minutes 3 times per week at 1 M. | 71.3 | 24 | 24 | 0 |
| 8 | Entire side for 15 minutes 3 times per week at 1 M. | 64.1 | 25 | 23 | -2 |
| 9 | Entire side for 15 minutes 3 times per week at 1 M. | 57.0 | 21 | 21 | 0 |
| 10 | Entire side for 15 minutes 3 times per week at 1 M. | 71.3 | 24 | 25 | +1 |
| 11 | Entire side for 15 minutes 3 times per week at 1 M. | 95.0 | 33 | 33 | 0 |
| 12 | Entire side for 15 minutes 3 times per week at 1 M. | 85.5 | 32 | 36 | +4 |
| 13 | Entire side for 15 minutes 3 times per week at 1 M. | 78.4 | 26 | 26 | 0 |
| 14 | Entire side for 15 minutes 3 times per week at 70 cm. | 87.3 | 21 | 19 | -2 |
| 15 | Entire side for 15 minutes 3 times per week at 70 cm. | 116.4 | 24 | 24 | 0 |
| 16 | Entire side for 15 minutes 3 times per week at 70 cm. | 145.5 | 31 | 36 | +5 |
| 17 | Entire side for 15 minutes 3 times per week at 70 cm. | 130.9 | 28 | 28 | 0 |
| 18 | Entire side for 15 minutes 3 times per week at 70 cm. | 101.9 | 17 | 33 | +16 |
| 19 | Entire side for 15 minutes 3 times per week at 70 cm. | 116.4 | 22 | 21 | -1 |
| 20 | Entire side for 15 minutes 3 times per week at 70 cm. | 130.9 | 24 | 24 | 0 |
| 21 | Entire side for 15 minutes 3 times per week at 70 cm. | 87.3 | 18 | 20 | +2 |
| 22 | Entire side for 15 minutes 3 times per week at 70 cm. | 145.5 | 34 | 29 | -5 |
| 23 | Entire side for 15 minutes 3 times per week at 70 cm. | 101.8 | 22 | 22 | 0 |
| 24 | Entire side for 15 minutes 3 times per week at 70 cm. | 145.5 | 22 | 22 | 0 |
| 25 | Entire side for 15 minutes 3 times per week at 70 cm. | 116.4 | 25 | 22 | -3 |
| 26 | Entire side for 15 minutes 3 times per week at 70 cm. | 145.5 | 24 | 23 | -1 |
| 27* | Wound (locally) for 15 minutes 3 times per week at 70 cm. | 58.2 | 17 | 17 | 0 |
| 28* | Wound (locally) for 15 minutes 3 times per week at 70 cm. | 145.5 | 22 | 20 | -2 |
| 29* | Wound (locally) for 15 minutes 3 times per week at 70 cm. | 101.9 | 16 | 20 | +4 |

*Animal kept in complete darkness except when irradiated.

the fourth (No. 60) showed a difference of nine days. This difference of nine days is exceeded by only 3 of the irradiation experiments (Nos. 18, 33, and 40) and equalled by 1 (No. 30).

The variability of the results in all groups makes them difficult to evaluate. No one of the irradiation procedures can be selected as being definitely superior. Groups 30 through 33 showed 3 well-benefited wounds and 1 (No. 32) that was definitely retarded. The same amount of radiant energy per unit time, administered locally, in Groups 34 through 37, showed no difference in healing time in the four

TABLE II

LARGE WOUND EXPERIMENTS

(LEFT WOUND IRRADIATED, RIGHT WOUND CONTROL)

| EXPERIMENT NUMBER | IRRADIATION PROCEDURE | TOTAL RADIANT ENERGY RECEIVED IN GM. CALORIES PER SQ. CM. | HEALING TIME IN DAYS | | DIFFERENCE |
|---|---|---|---|---|---|
| | | | LEFT | RIGHT | |
| 30 | Entire side for 15 minutes 3 times per week at 70 cm. | 145.5 | 28 | 37 | +9 |
| 31 | Entire side for 15 minutes 3 times per week at 70 cm. | 174.6 | 32 | 38 | +6 |
| 32 | Entire side for 15 minutes 3 times per week at 70 cm. | 232.8 | 38 | 32 | -6 |
| 33 | Entire side for 15 minutes 3 times per week at 70 cm. | 189.5 | 31 | 45 | +14 |
| 34 | Wound (locally) for 15 minutes 3 times per week at 70 cm. | 130.9 | 27 | 27 | 0 |
| 35 | Wound (locally) for 15 minutes 3 times per week at 70 cm. | 160.0 | 29 | 29 | 0 |
| 36 | Wound (locally) for 15 minutes 3 times per week at 70 cm. | 174.6 | 29 | 29 | 0 |
| 37 | Wound (locally) for 15 minutes 3 times per week at 70 cm. | 174.6 | 38 | 38 | 0 |
| 38 | Wound (locally) for 5 minutes 6 times per week at 70 cm. | 145.5 | 36 | 35 | -1 |
| 39 | Wound (locally) for 5 minutes 6 times per week at 70 cm. | 116.4 | 28 | 33 | +5 |
| 40 | Wound (locally) for 5 minutes 6 times per week at 70 cm. | 130.9 | 35 | 46 | +11 |
| 41* | Wound (locally) for 5 minutes 6 times per week at 70 cm. | 116.4 | 28 | 28 | 0 |
| 42* | Wound (locally) for 5 minutes 6 times per week at 70 cm. | 140.6 | 31 | 33 | +2 |
| 43* | Wound (locally) for 5 minutes 6 times per week at 70 cm. | 160.1 | 38 | 41 | +3 |
| 44* | Wound (locally) for 5 minutes 6 times per week at 70 cm. | 150.4 | 39 | 34 | -5 |
| 45* | Wound (locally) for 5 minutes 6 times per week at 70 cm. | 169.8 | 46 | 43 | -3 |
| 46* | Wound (locally) for 15 minutes 3 times per week at 70 cm. | 160.1 | 32 | 36 | +4 |
| 47* | Wound (locally) for 15 minutes 3 times per week at 70 cm. | 189.2 | 31 | 33 | +2 |
| 48* | Wound (locally) for 15 minutes 3 times per week at 70 cm. | 247.4 | 40 | 44 | +4 |

*Animal kept in complete darkness except when irradiated.

experiments. Groups 46 through 48 also received the same amount of radiant energy locally per unit time and were also kept in the dark between treatments to more specifically irradiate the experimental wound. Though all three showed positive effects none of the differences were marked.

TABLE III

NONIRRADIATION EXPERIMENTS

| SMALL WOUNDS | | | | LARGE WOUNDS | | | |
|---|---|---|---|---|---|---|---|
| EXPERIMENT NUMBER | HEALING TIME IN DAYS | | DIFFERENCE | EXPERIMENT NUMBER | HEALING TIME IN DAYS | | DIFFERENCE |
| | LEFT | RIGHT | | | LEFT | RIGHT | |
| 49 | 24 | 24 | 0 | 54 | 35 | 39 | 4 |
| 50 | 29 | 29 | 0 | 55 | 42 | 37 | 5 |
| 51 | 28 | 28 | 0 | 56 | 38 | 41 | 3 |
| 52 | 34 | 31 | 3 | 57 | 43 | 43 | 0 |
| 53 | 27 | 27 | 0 | 58 | 28 | 28 | 0 |
| | | | | 59 | 29 | 29 | 0 |
| | | | | 60 | 46 | 55 | 9 |

The average healing time of the 10 nonirradiated small wounds (Table III, left) was 28.1 days; of the 29 directly irradiated small left wounds (experimental) (Table I), 20.9 days; and of the 29 indirectly irradiated small right wounds (control) (Table I), 21.7 days. A similar comparison of all the large wounds shows an average healing time for the 14 nonirradiated wounds (Table III, right) of 38 days; for the 19 directly irradiated left wounds (Table II) of 33.5 days; and for the 19 indirectly irradiated right wounds (Table II) of 35.8 days. This indicates a mild acceleration in the healing rate of the wounds in the irradiated animals, the indirectly irradiated right wounds, which received only the general systemic effect, showing relatively less acceleration than those directly irradiated.

## SUMMARY

The rate of healing of 60 pairs of experimental wounds in dogs has been studied. In 48 of the experiments (29 small, 255 sq. mm.; and 19 large, 1,256 sq. mm.), the left wound was irradiated with a carbon arc lamp. Various amounts of radiant energy were given in different groups. In some the entire side of the body, in others only the wound was irradiated. Some of the animals were kept in complete darkness between irradiations.

In the 29 small wound experiments, 8 of the irradiated wounds showed acceleration, 8 retardation, and 13 no difference in healing rate when compared to its control.

Of the 19 large wound experiments, 10 showed acceleration, 4 retardation, and 5 no difference in healing rate when compared to its control.

In 5 small wound experiments in which no carbon arc radiation was given, only 1 slight healing time difference was found. In 7 large wound nonirradiation experiments, 4 showed slight to moderate differences.

## CONCLUSION

Carbon arc irradiation, of the type and dosage used, has but little accelerating effect on the healing of clean wounds in the dog.

This study was suggested to me by Prof. Henry Laurens.

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# Editorials

## The Surgical Treatment of Carcinoma of the Breast

ONE of the more interesting developments in surgical therapy during the last decade or so is the apparent casualness of many operators in regard to the radical removal of the breast in cases of carcinoma of that organ. This rather nonchalant attitude varies from the performance of, a mere local excision of the malignant tumor itself, a simple mastectomy, or a hurried inadequate and incomplete dissection of the chest wall and corresponding axilla. When questioned as to the reason for this relaxation from the rigid technique of meticulous and radical extirpation of the breast and its contiguous structures, the various surgeons will make the rather naïve reply that "the operation is less mutilating and besides radiation therapy will take care of local recurrences!" The question of the efficacy of pre- or postoperative radiation therapy in the treatment of malignant tumors of the breast has nothing whatever to do with the proper or improper *surgical* care administered to a patient affected with such a tumor. In our present state of knowledge radiation therapy, either deep x-ray or radium, although a most important adjunct, does not justify the slightest lessening in the thoroughness or the radicalness of the operative removal of the malignant breast with its associated structures of the pectoral and corresponding axillary regions. The diffusion of information concerning breast tumors through the lay press and periodicals has made it possible to see these cases at such an early stage of the disease that a definite preoperative diagnosis often cannot be made, thus never before has the opportunity for the success of the surgical cure of this malady been so favorable or opportune. The general characteristics and technique of the operation for the radical amputation of the breast have been developed over a period approximating one hundred years and this operation today may be considered, more than almost any other in surgery, one that is standardized. Years of clinical, pathologic, and surgical research revealing the clinical course of this disease, its paths of invasion in the breast and its surrounding structures, the location and frequency of its metastases, implantations and recurrences, the method of operating from the simplest and most conservative to the most radical removal, have all played an important rôle in the development of this universally recognized surgical procedure. It is certainly one operation upon which the majority of well-trained, thinking surgeons are in full agreement

the world over; and yet, paradoxic as it may seem, this operative procedure today is, generally speaking, not carried out or performed as well as it was twenty years ago. One reason for this regression of the operative procedure would seem to be due to a total lack of conception of the true principles upon which the surgical attack is based and the ends it is supposed to attain and/or a lack of technical ability on the part of the surgeon. After all the operation is a surface one which, because of the low mortality associated with it, may be performed in any sort of an offhand, least troublesome manner, the operative field being covered, in the majority of instances, with skin flaps which heal up promptly and thus conceal all evidence of a lack of thoroughness and incompetence at the time of operation. It would, of course, be impossible to prove that a more careful operation, in an individual instance, would have prevented a local return of the disease, but it can be stated without reservation that the percentage of local recurrence of this malady is far less in the hands of those surgeons who take pride in the perfection of their dissections in these cases. The operator should be held responsible only for the postoperative recurrence of the disease within the local limits of the operative field and not for remote metastases. All that can be expected of such an operation is to remove and cure the disease locally and this would seem to be the only yardstick by which one can measure the success or failure of any surgeon attempting to treat malignant tumors of the breast.

In the reports of postoperative studies published by many different observers in this country and abroad, the majority of local recurrences following radical amputation of the breast have taken place at some point within the skin overlying the operative field. When one considers the embryologic development of the breast, together with the arrangement, location, and drainage of the lymphatic capillaries in the skin and into the subcuticular lymphatic plexus, it is not to be wondered that so many recurrences take place in the skin. The mammae are ectodermal in origin growing from a knoblike thickening of ectoblast of the embryo down into the underlying mesoblastic tissue. This ectoblastic ingrowth represents a sunken area of integument that in principle corresponds to the marsupial pouch of the lowest mammals (monotremes). Solid epithelial sprouts grow out from the sides of the conical- or flask-shaped epidermal plug and are the first anlages of the true mammary gland, later becoming the excretory ducts. Subsequently the central part of the ectoblastic ingrowth undergoes degeneration and destruction, and what at first was an elevation now becomes a depression of the surface. From the middle of this depressed area there appears about the time of birth an elevation that later becomes the nipple. Meanwhile, the epithelial duct outgrowths penetrate the surrounding condensed mesoblastic stroma, increase in length,

subdivide, and acquire a lumen at their expanded distal ends, thus giving rise to the systems of ducts and lobules of immature gland tissue. With the further development of the latter, the surrounding mesoblastic stroma is broken up into the interlobular septa and fibrous framework of the corpus mammae. Naturally, the lymphatic vessels which develop simultaneously with the gland parenchyma accompany the downgrowth of the original ectoblastic pouch and thus the deeper lymph vessels surround the groups of alveoli as channels that lie within the interlobular connective tissue and pass toward the surface where they form the rich subareolar plexus. The latter also receives the collecting stems from the close cutaneous networks that drain the integument covering the nipple, areola, and the skin overlying the dome of the breast. In addition to a few trunks that follow the perforating arteries and become afferents of the lymphatic nodes lying along the internal mammary artery, all the lymphatics of the breast join to form two or three large trunks that pass from the lower and lateral borders of the organ through the subcutaneous tissue toward the axilla to empty into the axillary glands.

It would seem possible that the most important tissue to remove in a radical amputation of the breast is the skin. This reasoning is based upon the anatomic facts mentioned above. The basin, so to speak, which receives the greatest lymph drainage from the breast is the subareolar and subcuticular plexus underlying the skin covering the dome of the breast. The breast is an appendage of the skin and the first spread of carcinomatous cells will be along the lymphatic channels toward the subareolar plexus. A resection of skin theoretically as extensive and wide as that of the underlying muscle and fascia layers would be ideal but, of course, impractical; yet the least that should be done is the complete removal of the entire skin covering the dome of the breast. In addition, the circular incision should be extended sufficiently to include the newgrowth and not the nipple as the center of the circle. The most important by far of the three layers of tissue, i.e., skin, fascia, and muscle, is unquestionably the skin. When a local recurrence takes place in the skin, it means the disease has persisted uninterruptedly since before operation and that either the operator did not get beyond it at the time of operation and cut through the growth or that the tumor had grown further in the skin than he anticipated. In either event his margin in the skin was too narrow and the new manifestation of the tumor is merely a persistence of a growth that was there at the time of operation and not a recurrence of the disease at some period following operation. Even a cursory examination of the skin incisions used today that will allow the operator to close the operative defect after removal of the breast show that the amount of skin sacrificed is totally inadequate. In the

line of the incision above and below the tumor the elliptical area of skin removed is perhaps sufficient; but on the sides, in order to bring the skin flaps together, the margin is far too small. The great frequency of the postoperative out-cropping of the disease along the line of the incision bears ample witness to this error.

Emphasis should be laid upon the point that the layer of skin is the most vital to the ultimate success or lack of it following radical amputation of the breast for a malignant tumor, and further that this layer of integument should be removed thoroughly and radically without the slightest regard by the operator for closure. The remaining defect can be covered by skin grafts either at the time of operation with Thiersch grafts, or, in the event that the operator is not acquainted with the technique of cutting these, small Revenolin grafts may be placed upon the granulating wound some days later. The importance of a wide excision of the skin has never been sufficiently emphasized, although Halsted taught and wrote about this feature continuously during his lifetime. It is important to realize that the skin cannot be thought of as an outer garment existing merely to cloak the operative field and to be cut accordingly in order to fit as perfectly as possible; but on the contrary it must be regarded as a dangerous infested maze of potential disease to be got rid of with no thoughts of closure or cosmetic results. Lack of patience to learn how or to perform a meticulous dissection in the execution of a radical extirpation of the breast, speed in operating because of the feeling that to be slow and careful is to be considered somewhat less dexterous, and finally being concerned about short postoperative hospitalization, avail patients very little solace when the one chance they had to be rid of their disease has been sacrificed because of ignorance or carelessness or both.

—*William F. Rienhoff, Jr.*

## "Canned" Blood Transfusion

THERE is probably no other place in the world today where blood transfusion is being more extensively studied than in Soviet Russia. From these intensive investigations there has recently emerged the practice of transfusing stored cadaver blood. Whereas previously blood from all healthy "donors" was employed, more recently it has been found that the more suitable cadavers are those of persons dying suddenly; for example, as a result of coronary thrombosis, electrocution, cerebral hemorrhage, or traffic accidents. This is due to the curious but unexplainable phenomenon that, whereas such blood rapidly coagulates if removed in the first few hours after death, in from one-half to one and one-half hours it "disagulates" by supposedly undergoing fibrinolysis and remains fluid. The practical sig-

nificance of this accidental discovery is that such blood can be conserved without the addition of an anticoagulant. Under aseptic precautions from 2 to 3.5 liters of blood is obtained from the jugular veins of each cadaver and after necessary bacteriologic and serologic tests have been done, the blood is hermetically sealed and stored at a temperature not greater than 4° C. Because fragility of the red blood cells with subsequent hemolysis increases markedly after the tenth day, it is rarely used after this period.

According to these investigators, experience in over 1,000 cases has demonstrated that these transfusions can be done with comparative safety. The Russian advocates further claim that in addition to its economic advantages emergency transfusions can always be easily and quickly performed. However, it is of interest that they do not advocate replacing present-day methods by this procedure. Further analysis of their 1,000 cases reveals the disturbing fact that the incidence of reactions was 21 per cent and fatalities 0.7 per cent. At present any method of transfusion which gives untoward reactions in over 1 per cent of the cases should not be considered sufficiently developed for universal adoption. Whereas such a method may have economic advantages in Soviet Russia, at the present time justification of its use here can hardly be considered warranted. However, it promises a fruitful field of utilization during warfare.

Whereas in this country a somewhat parallel method has been developed, the blood is obtained from living donors. The method consists essentially of withdrawing approximately ½ liter of blood from every suitable patient and visiting relatives in the hospital, adding citrate solution as an anticoagulant, and after proper serologic and bacteriologic examinations "depositing" it in the "blood bank." Withdrawals are then made against each "ward account" as the necessity arises. Whereas the transfusion of conserved blood may be considered justifiable and therapeutically advantageous in large charitable institutions, such a method, because of its departure from the physiologic ideal, can never displace the transfusion of unmodified blood.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## THE HORMONAL BASIS OF THE ETIOLOGY AND TREATMENT OF PROSTATIC HYPERTROPHY

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THE TREATMENT of hypertrophy of the prostate has been chiefly surgical. With the increasing knowledge regarding the sex hormones and their interrelationship, however, new ideas have arisen regarding the etiology and possible treatment of this condition. The purpose of this paper is to review the present ideas of hormonal balance in prostatic hypertrophy as well as to analyze the current concepts of endocrine therapy in this disease.

### PATHOGENESIS OF HYPERTROPHY OF THE PROSTATE

One is impressed in a review of the literature by the confusing and contradictory descriptions by various authors of the normal and pathologic anatomy of the prostate. When anterior, posterior, lateral, and median lobes are mentioned, authors may refer to the embryologic divisions of the prostate described by Lowsley[1] but not distinguishable in the normal adult; or they may refer to the situation of the hypertrophied lobule in relation to the lumen of the prostatic urethra. One of the most recent reviews of the literature of the anatomy and pathologic physiology of the prostate is that of MacCallum.[2] He states that most students of the subject are in agreement that hypertrophy of the prostate affects essentially the "proximal median lobe, and in many cases the subcervical glands of Albarran, while the posterior or distal dorsal lobe, the lateral lobes and the anterior or ventral lobes are not usually involved." The introduction of this new terminology, however, while perhaps more correct anatomically, only adds to our confusion. The work of Randall concerning the pathologic anatomy of prostatic hypertrophy is well known and generally accepted. He believes that hypertrophy of the prostate may originate in any lobe, with the possible exception of the true posterior lobe. Thus, the glandular tissue of the right or left lateral lobes, the glands of the anatomic middle lobe or posterior commissure, and the subcervical gland of Albarran may share in hypertrophic proliferation; and any one or combination of these may be the seat of origin of the growth.

Received for publication, Dec. 3, 1937.

Concerning the so-called middle-lobe enlargement, there are two different glandular elements situated in the midline posteriorly which may give rise to this enlargement: the posterior commissural glandular tissue and the subcervical glandular tissue of Albarran. The posterior commissural tissue is the anatomic middle lobe, a definite mass of glandular tissue contiguous with the lateral lobe sharing with it the true prostatic capsule and not showing any separating capsule or fibers.

Deming, Jenkins, and van Wagenen have confirmed Randall's ideas and believe that hypertrophy of the prostate usually springs from one of two distinct tissues: (1) the lateral lobes and "pre spermatic lobe"; and (2) the submucosal glands of the posterior urethra and trigone. Deming and his coworkers believe that the submucosal glands give rise to 50 per cent of hypertrophied prostates in man. The direction of expansion would determine then whether the hypertrophy was lateral, median, etc. It is interesting to note that the above authors found that castration has no effect upon the submucosal glands in the prostatic urethra and trigone of the rat.

MacCallum has reviewed the ideas regarding the nature of prostatic hypertrophy. Virchow, Aschoff, and others believed that it was neoplastic: adenoma, fibroadenoma, or fibromyoma. Reischauer thought that it was a fibroepithelial growth related to myoma of the uterus, which is interesting from a hormonal point of view. The presence of smooth muscle among the proliferating glandular elements has been thought to argue strongly against the process being neoplastic (MacCallum).

In comparing the clinical and experimental hypertrophies of the prostate, it has been noted that: (1) the seminal vesicles share in the experimental but not in the clinical hypertrophies; (2) hypertrophy of the smooth muscle is much more prominent experimentally than clinically; (3) the epithelial elements which hypertrophy in the rat's prostate are usually squamous, while those in the human prostate are glandular. It may be questioned whether the clinical and experimental hypertrophies of the prostate are analogous, but the differences may be due to dissimilarities in time, hormones, and species.

Infection and arteriosclerosis also have been considered to be etiologic factors in hypertrophy of the prostate. Recent advances in the field of endocrinology have shown that the prostate is under hormonal control, and it has been suggested that enlargement of the prostate may be due to a disturbance in endocrine balance.

### SEX HORMONES OF PITUITARY, TESTIS, AND PROSTATE

It is an established fact that there is an hormonal balance among the hypophysis, testis, and prostate. However, our knowledge concerning this interrelationship is not complete, and the vast literature on hor-

mones has often been more confusing than enlightening. The first step in the elucidation of this relationship is the separation of the component hormones.

*1. Testicular Hormones.*—While Berthold in 1849 demonstrated that the testis had an internal secretion, it was not until 1927 that the first successful extraction of a hormone from testicular tissue was performed (McGee). Butenandt in 1931 crystallized the male hormone, androsterone, from human urine; in 1934, Ruzicka synthesized androsterone from cholesterol. Another male hormone, testosterone, was prepared from fresh testicular tissue by Laqueur and coworkers in 1935; this same substance and others with androgenic activity have been synthetically prepared. It is known that the chemical and experimental properties of testosterone and androsterone are different. The number and specific nature of other male hormones are unknown. (See reviews of Koch and of Moore and Price.)

*2. Hypophyseal Hormones.*—From the work of Aschheim and Zondek, Smith and Engle, Evans and others, at least two gonadotropic hormones of pituitary origin are known. One causes maturation of the ovarian follicle, with the resultant production of the ovarian hormone, theelin, which prepares the uterine mucosa for the reception of the ovum. The other causes luteinization of the remains of the ruptured ovarian follicle, the corpus luteum, which in turn secretes a hormone, progestin, causing growth of the fertilized ovum, decidual and placental formation. In pregnancy, a hormone, prolan, closely resembling the second gonadotropic hormone of the pituitary, is secreted in the urine together with theelin.

In the male rat, Hisaw and others found that the follicle stimulating hormone stirred proliferation of the germinal epithelium alone, while the luteinizing hormone acted in the interstitial cells and caused enlargement of the accessory sex organs, apparently through the male sex hormone secreted by the hypertrophied interstitial tissue. The enlargement was intensified by the simultaneous action of the two hormones. Recently Evans and his associates described the separation of a third gonadotropic hormone which stimulates the Leydig cells of the testis. The importance of this possible hormone in explaining hypertrophy of the prostate will be discussed later.

*3. Prostate.*—No definite prostatic hormones have been isolated.

### EFFECT OF MALE HORMONE ON THE PROSTATE AND THE HYPOPHYSIS

Castrates have underdeveloped prostates; to bring about maximal reduction in size of this gland, castration must be performed early in life. MacCallum points out that neither the effect of castration on the different lobes of the prostate and the accessory periurethral, subcervical, or trigonal glands, nor the effect of the internal secretion of the testis on

the different parts of the prostate is known. The knowledge of these effects might be helpful in judging the benefits to be derived from hormonal therapy in prostatic hypertrophy.

A definite pituitary hypertrophy follows castration. Korenchevsky and coworkers and McCullagh and Walsh found that injections of male hormone restored the prostate to normal but did not control the pituitary hypertrophy in castrates. The latter investigators also found that if a castrated and a normal animal, usually the rat, were joined in parabiosis, and if then a testicular mush was injected into the castrated partner, pituitary activity was controlled and one did not find prostatic enlargement in the normal animal. In control experiments where a castrated rat was united in parabiosis with a normal animal, prostatic hypertrophy, as determined by glandular weight, resulted in the normal partner (McCullagh and Walsh). From these and other experiments, McCullagh and coworkers evolved the hypothesis that the internal secretion of the testis is of a dual nature. One substance extracted by organic solvent and believed to have its origin in the interstitial tissue is called androtin; the other substance, which is water soluble and supposed to be secreted by the cells of the seminiferous tubules, has the properties of an inhibiting chalone and is called inhibin.

The results of Lower and others suggest that the injection of the lipid-soluble fraction of the testis into a normal rat causes hypertrophy of the prostate, while the injection of the water-soluble extract causes atrophy of the gland.

### THE EFFECT OF THE PITUITARY GLAND ON THE TESTIS AND PROSTATE

Following hypophysectomy there is atrophy of the testis and accessory sex glands which can be completely repaired by reimplantation or injection of pituitary substance (Smith and Engle, Evans and Simpson). Adequate doses of male sex hormone will prevent atrophy of the accessory sexual organs in hypophysectomized as well as in castrated rats (McCullagh and Walsh, Zuckerman and Parkes). Urinary androgens will maintain the normal appearance of the testis in hypophysectomized rats; pituitary extracts, the pituitary-like hormones from the urine and yeast, will do the same thing. If there is already atrophy of the rat testis following hypophysectomy, urinary androgens will not repair this degeneration; however, pituitary extracts will restore the appearance of the atrophic gonad to normal (Martins and Rocha, Hisaw, Nelson, Leonard, McCullagh).

From the results of injecting anterior pituitary-like substance and parabiosis experiments, it is known that pituitary hyperfunction may cause prostatic hypertrophy (McCullagh and Walsh). The best evidence of pituitary hyperfunction that is known to date is the presence of the gonadotropic hormone in the urine. There are at least six sources

of gonadotropic hormone: (1) the anterior lobe of the pituitary; (2) prolan or the anterior pituitary-like substance of pregnancy urine; (3) urine of men with testicular tumors (Aschheim and Zondek, Ferguson, and Hinman); (4) the urine of male castrates; (5) urine of some cryptorchids (Hess and others); and (6) urine of some normal men (cyclic) (Harris and Brand). Whether these hormones are one and the same has been debated (see Hinman's review).

Castrates, although showing gonadotropic substance in the urine, do not have prostatic hypertrophy as there is no testicular tissue to act as an intermediary. The question arises: Do patients with malignancy of the testis with gonadotropic hormones in the urine have enlargement of the prostate? Teems found three cases of interstitial cell tumor of the testis associated with either normal or atrophic prostatic gland and a case of carcinoma of the "genitaloid" cells of the testis accompanied by practically an absence of interstitial cells in a man sixty-five years of age with a hypertrophied prostate. There is no mention of the presence or absence of gonadotropic substance in the urine of these patients. Ferguson in 1933, in a study of 117 cases of teratoma testis, noted diffuse enlargement of the prostate of seminal vesicles accompanied by hyperplasia of the interstitial cells of the opposite testicle, varying in degree with the amounts of anterior pituitary-like substance recovered from the urine. As Geschickter points out, however, clinical hypertrophy of the prostate is usually focal rather than diffuse; therefore, it cannot be assumed that hormonal control of normal and of pathologic growths are identical. Greulich and Burford report three cases of testicular tumors in cryptorchid dogs associated with prostatic metaplasia, mammary and other sex changes. In this connection it would be interesting to know if hypertrophy of the prostate ever occurs in old untreated cases of bilateral cryptorchidism. There is no series mentioning this in the available literature. Braasch states that in cryptorchidism there is rarely an accompanying enlargement of the prostate gland.

### EFFECT OF THEELIN ON THE PROSTATE

The injection of theelin into animals causes metaplasia and keratinization of the epithelium of the utricle of the prostate, enlargement of the prostate due to increase of the stroma, and increase in size of seminal vesicles (Moore and Price, De Jongh, Zuckerman and Parkes, and MacCallum). These effects can be neutralized by the injection of the male sex hormones (Wells, Zuckerman and Parkes, and De Jongh). The urine of normal men contains theelin (or a theelin-like substance) and male hormones; however, the variations in the amounts of these two substances in the urine under normal and pathologic conditions is but little known. Improper balance between the male and female sex hormones has been the basis for one theory of prostatic hypertrophy

(Laqueur), as well as a possible explanation for the etiology of prostatic cancer. This latter statement gets some support from our knowledge of the effect of ovarian hormone on breast tumors.

SOURCES OF THE MALE AND PITUITARY HORMONES: HISTOLOGIC EVIDENCE

*1. Male Hormones.*—The Leydig cells of the testis are considered to be the source of the male hormone. This inference is made from observations on the cryptorchid testis, the testis treated by x-ray, and atrophic and hypertrophied testis. In the undescended testis the seminiferous tubules are atrophic, the Sertoli cells are distended with fat, while the cells of Leydig are normal or hypertrophied. The secondary sex characteristics develop normally in most bilateral cryptorchids. Similarly in the testis treated by x-ray therapy, the Sertoli cells and interstitial cells of Leydig remain normal, although the Sertoli cells may be fat-ladened. Hanes found the Sertoli cells to be constantly present in the atrophic testis and could not be sure whether they or the Leydig cells were the hormone-producing cells. However, since compensatory hypertrophy occurs in the Leydig cells when one testis has been removed and not in the Sertoli cells, he believed that the Leydig cells probably produce the secretion. Since both types of cells are usually present under most pathologic conditions, the exact rôle of each has not been ascertained (Oslund). It is possible that both have an internal secretion.

McCullagh believes that the male sex hormone, androtin, is comparable to theelin, but MacCallum believes that the watery extract of the germinal epithelium, inhibin, is more analogous to theelin, since androtin cannot cut short the excessive secretion of the hypophysis. MacCallum makes a further interesting suggestion: while inhibin restores the hypophysis to quiescence or stops or diminishes the production of gametokinetic hormone, it seems that this quiescence must also stop a second and different gonadotropic hormone which, like that which stirs the formation of the corpus luteum in the female with the production of progestin, stirs the interstitial cells of the testis to produce lipoid-soluble male hormone causing hypertrophy of the prostate. It seems important to recognize such a second gonadotropic hormone in the male comparable to the luteinization gonadotropic of the female and to note evidences of its formation in the cells of the hypophysis in cases of prostatic hypertrophy (MacCallum).

*2. Pituitary Hormones.*—One gonad-stimulating hormone seems to come from the basophilic cells of the hypophysis. In castrates or cryptorchids these cells increase in number, swell, and become vacuolated. These changes can be reversed by the injection of theelin, watery extracts of the testis, but not by the male sex hormone or synthetic testicular hormone (Martins and Rocha, Nelson, McCullagh, and Leonard and Hisaw). The exact origin of the second gonadotropic hormone from the hypophysis is not clear. The large, slightly eosinophilic preg-

nancy cells of Erdheim and Stumme have been suggested as the source, as these cells appear during the time progestin is liberated (MacCallum). Whether there are cells in the hypophysis of the male resembling those in pregnant females is unknown. The recent work of Evans and others describing a third gonadotropic hormone which stimulates the Leydig cells of the testis increases the field of speculation. Certainly our knowledge of the physiology of the pituitary hormones is greater than that of their anatomic sources.

### THEORIES OF ETIOLOGY OF PROSTATIC HYPERTROPHY ON HORMONAL BASIS

From their experimental work, Lower, Engel, and McCullagh postulated a theory for the cause of prostatic hypertrophy. They believed that the gonadotropic hormone of the anterior lobe of the pituitary gland would overstimulate the secretion of androtin unless held in check; normally the spermatogenic cells are supposed to secrete enough inhibin to prevent excessive secretion of the pituitary hormone. With degenerative changes or decreased function of the spermatogenic cells, as in old age, there would be a supposed reduction in the amount of inhibin to such a degree that the functional activity of the pituitary gland would be unrestricted. As a result, excessive male hormone would be secreted and prostatic hyperplasia would develop. The Cleveland clinicians cited a series of seventy-six cases of prostatic hypertrophy which were treated by the oral administration of desiccated testicular substance; 63.1 per cent of these patients were subjectively improved. In none was there any demonstrable change in the size of the prostate. It will be noted that it was the whole testicular substance and not the water-soluble fraction (inhibin) which was used in this study.

While the above hypothesis is novel and provocative of thought, it has been criticized in that: (1) conclusions were drawn from the results of too few animal experiments; (2) impure substances were used; and (3) the histologic evidence is unconvincing in regard to the relative functional capacity of the interstitial and tubular tissues of the testis in prostatic hypertrophy. Teems found that not infrequently a good state of preservation of the seminiferous tubules and spermatogenesis is encountered between the ages of forty and eighty-nine years. Also, he found that there is a steady decrease in the number of interstitial cells in the later decades of life. Braasch believes that the absence of any convincing morphologic evidence of increased function of the interstitial cells or diminished function in the tubules during the period of prostatic hypertrophy gives only negative evidence as to their functional capacity in the secretion of autacoids.

It would be difficult to try to explain by the above theory the absence of hypertrophy of the prostate in cases of cryptorchidism or those in which the testes are injured by x-ray therapy. In such cases there is a lack or diminution in the amount of germinal epithelium and a relative

increase in the amount of interstitial tissue, which should be an ideal combination for hypertrophy of the prostate according to Lower, Engel, and McCullagh's hypothesis.

Contrary to the above view, Laqueur believes that in prostatic hypertrophy there is an improper balance between the male and estrogenic hormones, hence the abnormal changes leading to prostatic hypertrophy. Laqueur reported improvement in two-thirds of 133 cases of prostatic enlargement treated by male hormone therapy. As Koch points out, however, there have been so few studies on the rate of secretion of male and estrogenic hormones in the normal male, much less in cases of prostatic hypertrophy, that the whole subject should be considered in the experimental stage until more conclusive evidence is obtained. Hamilton, Heslin, and Gilbert found that in a series of nine men with a slight amount of residual urine, nocturia, and other sequelae induced by prostatic hypertrophy, there was no intensification of the symptoms upon prolonged treatment with estrogenic substances (500 to 1,500 I.U. theelin in oil over a period of twenty-six days). Furthermore the good results in the treatment of hypertrophy of the prostate by the administration of male hormones are hard to explain unless one postulates some anti-male hormone effect to be present, since male hormones, at least the lipid-soluble fraction of the testes, cause hypertrophy of the prostate in experimental animals.

### INDIRECT SURGICAL PROCEDURES IN THE TREATMENT OF PROSTATIC HYPERTROPHY

*1. Castration.*—White in 1893 found that in castrated dogs there was uniformly atrophy of the glandular and then of the muscular elements of the prostate. Of 111 clinical cases of prostatic hypertrophy treated by castration, there was a high percentage (87 per cent) showing symptomatic improvement as well as clinical and histologic reduction in size of the prostate. However, castration is such drastic treatment that it is doubtful if many patients would submit to such a procedure, even if it were of proved value in the treatment of prostatic hypertrophy. Moreover, Deming, Jenkins, and van Wagenen found that in rats and monkeys the submucosal glands in the former and the mucosa of the posterior urethra in the latter were not affected by castration. They believe that there is no histologic evidence that the action produced by castration influences the growth of prostatic hypertrophy.

*2. Vasoligation.*—Theoretically one would expect little result on the prostate from vasoligation as histologically there is little change in the testes by such a procedure (Moore). Morson says that clinically division of the vas deferens per se has no effect on the size or function of the prostate. In his review Wolfson found that vasectomy alone was worthless in reducing the size of the enlarged prostate. Hada and Gotzl found no change in the dog's prostate after tying or cutting the

vas deferens. There is no large series reported in the available literature where vasoligation alone has been used in the treatment of prostatic hypertrophy. It is usually used as a prophylactic procedure against epididymitis when surgery of the prostate is contemplated. It would be interesting to examine the prostates of a large series of men who had had vasoligation years before for other reasons and compare the size of the gland with that of a group of normal men in the same age group.

*3. X-ray Therapy to Testis.*—Lower and Johnson from studies on the effect of deep x-ray therapy directed on the testes of dogs suggested that this may be of some value in reducing the size of the prostate. However, MacCallum quotes several authors who find that the secondary sex organs are unchanged after x-ray injury to the testis. Since the germinal epithelium is destroyed by x-ray therapy and the interstitial cells remain intact, one would expect, theoretically at least, that irradiation of the testis would be of little value in reducing the size of the prostate. Observations of such patients over a long period of years would be necessary, however, to judge the end-result and the efficacy of this treatment. Recently Geschickter has reported that in the monkey prostatic hypertrophy, which can be produced by the injection of anterior pituitary-like hormone, can be inhibited by irradiation of the testis.

### THERAPEUTIC APPROACHES TO THE HORMONAL TREATMENT OF PROSTATIC HYPERTROPHY

It is in the case of prostatic hypertrophy with little urinary frequency, occasional nocturia, low urinary residual in the bladder, and normal kidney function that endocrine therapy might do good, especially in a prophylactic sense. The production of experimental cryptorchidism in such patients by elevating the testis to the inguinal region or instead of ligating the vas deferens, the ligation of the vessels of the cord to cause testicular atrophy might be of value to attain this end. The end-results of x-ray therapy to the testis and vasoligation on prostatic hypertrophy need further clinical investigation. However, the difficulty of getting patients to submit to these procedures and the poor economy of such measures would make hormonic therapy more feasible and desirable.

According to our present knowledge, theoretically, suppression of the male hormone or the anterior pituitary gonad-stimulating substance should tend to prevent enlargement of the prostate. Whether this theory is correct or how to apply it in the clinical care of prostatic hypertrophy awaits further investigation.

It must be remembered in evaluating the results of treatment in prostatic hypertrophy that 50 per cent of men who develop prostatic enlargement never have obstructive symptoms and in a number who do the trouble is temporary (Hinman). Also, the psychic effects of any ther-

apy would have to be evaluated. The presence of infection, adenoma, or carcinoma in the prostate would add factors to complicate treatment, especially hormonal therapy. Since hypertrophy of the prostate takes years to develop, one should observe and probably treat the patient over a number of years before drawing conclusions. Certainly further data regarding the exact interrelation of the sex hormones will be necessary before a rational plan of treatment can be formulated. While one's enthusiasm must be tempered by skepticism, the day is possibly not far distant when hormonal therapy will supplant surgery in certain cases of prostatic hypertrophy.

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# Review of Recent Meetings

## REPORT OF THE PROCEEDINGS OF THE SURGICAL CONGRESS AT GOTHENBURG, JUNE 28-30, 1937

CARL SEMB, M.D., AND JOHAN STANG, M.D., OSLO, NORWAY

NORDISK Kirurgisk Forening (Nordic Association of Surgeons) held its twenty-first meeting at Gothenburg from June 28 to 30, 1937, with **Professor Sven Johansson** presiding.

Three main topics of discussion were on the program: (1) Cancer of the rectum; (2) examination of heart and vessels in relation to operation; (3) nonspecific affections in the lumbosacral region.

1. **Thv. Eiken,** of Aalborg, Denmark, submitted material collected in Denmark for the five-year period of 1931 through 1935. It included 1,444 cases, among which there were about twice as many men as women. Five per cent were under forty years of age, and more than one-half were above sixty years of age. In more than one-half of the cases the localization of the cancer was in the ampulla.

The extirpation by the sacral route in two stages was recommended as the routine method: first, performance of an iliac colostomy; six to eight weeks later, extirpation from below by the method of the German surgeon Goetze.

**Sam. Hybbinette,** of Stockholm, Sweden, presented his personal material on 243 cases with 113 radical operations, of which nearly all were abdominoperineal and of which 90 were performed in one stage. With regard to operability, as well as to mortality, there was a great difference between the hospital clientele (65 patients) and the private clientele (48 patients). In the group first named the operability was 38.4 per cent and the mortality 27.7 per cent, and in the latter group 70.5 per cent and 8.3 per cent respectively. The private patients had consulted a physician on an average of one-half year before the other patients. The figures, therefore, illustrate the importance of the early diagnosis. In his private clientele 40.4 per cent lived for ten years or more after the operation.

He criticized the fact that the cancer statistics reckoned with freedom from recurrence from the fifth year, while frequently metastases to the liver occurred just at that time. (Of 8 deaths in the fifth year after operation, 7 were due to metastases to the liver.)

**Elis Berven,** of Stockholm, Sweden, in the symposium emphasized that the difficulty of irradiation treatment lay in the fact that about 80 per cent of rectal cancers were radioresistant and that there was such a minimal difference between the dose which had effect on the tumor and that which damaged the normal mucous membrane.

Anorectal cancer of the squamous cell type in the first instance should have radiologic treatment. In desperate cases roentgenologic treatment should be given, because it effects cessation of hemorrhage, secretion, and tenesmus.

**G. Esbersen,** of Thisted, Denmark, had 22 cases of radical operation with no deaths. He used a personal modification of the abdominoperineal operation. The first stage was made fairly extensive with resection of the greater part of the sigmoid flexure. To avoid necrosis of the rectum, the superior hemorrhoidal artery was left intact. Rectum was removed in the second stage.

**R. Ingebrigtsen,** of Oslo, Norway, principally recommended abdominoperineal operation in one stage. He was of the opinion that none of the postoperative deaths after one-stage operation in his cases (5 of 28) could have been avoided by operation in two or more stages. Shock by the one-stage operation he attributed to hemorrhage. If hemorrhage was avoided or if blood transfusion was given, no severe shock was seen.

**G. Petrén,** of Lund, Sweden, had performed radical operation on 134 patients with cancer of the rectum in the period 1927 to 1936. Of these, 88 were operated upon perineosacrally with a mortality of 14 per cent. Forty-six were operated upon abdominosacrally with a mortality of 46 per cent. In spite of this difference in mortality Petrén recommended the combined operation, because he holds that the great immediate mortality was compensated by the very much better late results.

**P. Bull,** of Oslo, Norway, had for treatment from 1897 to 1937, 159 rectal cancer patients in all. Ninety of these were subjected to radical operation, 53 from below with a mortality of 7.3 per cent, and 35 combined with a mortality of 22.7 per cent. Thirty-one of these 35 were operated upon in two stages with a mortality of 13 per cent. The lecturer recommended the combined method in two stages; in the first stage, colostomy only.

Other statistics were reported by **Hans Bjerre,** and **Sv. Bagger,** Orebro, Sweden; **K. K. Nygaard,** Oslo, Norway; **E. Key,** Stockholm, Sweden; **Sven Johansson,** Gothenburg, Sweden; and **S. Søderlund,** Stockholm, Sweden.

The result of the majority of statistics was a considerably higher mortality by the abdominoperineal method than by the perineosacral method. A number of speakers recommended the centralization of these operations in a few hands.

2. In the discussion on the second topic **Johannes Ipsen,** of Sønderborg, Denmark, reported his investigations comprising partly the heart function, partly the peripheral vessels in operative patients.

In his reference to peripheral vessels he particularly dealt with the changes in the skin temperature. The temperature normally rose, when the anesthesia became effective, to more than 34° C. and remained constant (Group A). In certain cases there was deficient increase (Group B); or a secondary fall occurred during the anesthesia (Group C). The mortality was much higher statistically in Groups B and C than in Group A. Especially the patients who died shortly after the operation had abnormal charts. He further mentioned that the fall in the temperature of the feet could be stopped and the temperature made to rise again by intravenous injection of gum-saline solution.

**Abraham Troell,** of Stockholm, Sweden, gave an account of examinations of the heart in 287 thyreotoxic patients. In an abnormal roentgenogram of the heart and in an abnormal electrocardiogram he found that the operative mortality was increased, being three or four times as great as in normal findings.

**Eggert Møller,** of Hellerup, Denmark, as internist reviewer, stressed the fact that there was a great difference in the prognostic importance of the various diseases. Aortitis, myocarditis, and coronary sclerosis are the essential causes for operative mortality increasing with rising age.

Roentgenologic examination was the safest means of deciding whether, in a given case, an organic disease of the heart existed. This was due to the fact that the dilatation was the first compensatory step of the damaged heart.

The electrocardiogram was of particular importance in lesions of the myocardium. These would be revealed provided they were of essential significance to the preoperative diagnosis.

Electrocardiography was indicated in the presence of any case of arrhythmia, with the exception of the respiratory one, and it was further an indispensable link in every examination for the evaluation of the state of the heart in individuals over forty years of age.

**Torben Geill** and **J. Foged,** of Copenhagen, Denmark, had carried out electrocardiographic examinations on anesthetized patients and had found transient myocarditic changes.

**E. Svensgaard,** of Copenhagen, Denmark, and **Eggert Møller** of Hellerup, Denmark, elucidated the value of the electrocardiogram as compared with the other methods of examination carried out in 704 heart patients.

| | |
|---|---|
| The anamnesis alone revealed: | 20% of these cases |
| Inspection revealed further: | 4% of these cases |
| Stethoscopy revealed further: | 41% of these cases |
| Electrocardiography revealed further: | 21% of these cases |
| Roentgenologic examination revealed further: | 14% of these cases |

**H. Krieger Lassen,** of Copenhagen, Denmark, in addition to electrocardiography and roentgenologic examination, had carried out preoperative vital capacity tests. He had examined 359 patients. Even if only one of the tests—electrocardiography, roentgenologic examination, or vital capacity—deviated from normal, the mortality was 4.6 per cent greater than usual.

**J. Foged** found that electrocardiography revealed one-third of the latent heart diseases and made the operative prognosis safer. In a series of 1,049 patients he had a mortality of 0.50 per cent with normal electrocardiogram and 6.8 per cent with pathologic electrocardiogram. He was of the opinion that with the aid of electrocardiography one had arrived at a more accurate indication and a lower postoperative mortality.

**H. Brodersen,** of Oslo, Norway, had examined 100 operated patients electrocardiographically. In 48 were found pathologic changes; in 52, none. In both groups the mortality was equally high.

He criticized the reviewers because of their failure to classify the electrocardiographic patients into groups. In his own material he had distinguished between: (1) considerable, (2) small, but certain, and (3) uncertain electrocardiographic changes. Of the 48 patients with pathologic electrocardiograms, 21 belonged to Group 3, and in these no complications had occurred.

**Knud Nicolaysen,** of Drammen, Norway, reported electrocardiographic examinations in 400 operative patients over fifty years of age, which had revealed 4 cases of heart disease not diagnosed by the clinical examination. He maintained, therefore, that it was doubtful also whether electrocardiography would assist in reducing the postoperative complications.

**Johan Holst,** of Oslo, Norway, in a material of 374 cases examined had found 7, possibly primary, cardiovascular deaths. In 1 case only, however, was there correlation between the clinical findings before and after the operation and the postmortem findings.

3. In the discussion on nonspecific affections of the lumbosacral region, **R. Ingebrigtsen** had demonstrated in 20 patients (9 women and 11 men) unilateral sacralization as a cause of pain in the back. He emphasized that severe pain in patients with this lesion was always combined with contracture of the sacrospinalis muscle, as a rule scoliosis and arthrosis in the articulation between the transverse

process and massa lateralis of the sacrum, and in some cases spondyloarthrosis. The presence of unilateral sacralization without symptoms was found more frequently in men than in women.

The indication for treatment should be that no other demonstrable cause of pain was present. Further, the symptoms ought to be so severe that the patient was unable to work. Resection of the transverse process then would lead to cure.

**S. A. Brofelt,** of Helsingfors, Finland, in a series of 232 cases of low back pain, in which were not included polyarthritic and ankylopoetic lesions, had 42 unilateral sacralizations, 42 spondylolistheses, 8 spondyloses, 6 posterior displacements of vertebrae, and 29 cases of horizontal sacrum.

The lecturer discussed the importance of the angle between the sacrum and the lumbar column. The 29 cases with horizontal sacrum or sacrum acutum arcuatum all had more or less lumbosacral discomfort. The cause of this could be, he considered, the strain on the iliolumbar ligament.

He attached importance to the fixation by operation, including the three lower lumbar and the two upper sacral processes. The tibial graft was given a slightly angular shape so as to fit better into the lumbosacral curve. Confinement to bed for seven to twelve weeks and encasement in a plaster cast for eight to twelve months followed.

**Sig. N. Bakke,** of Bergen, Norway, as roentgenologic reviewer, reported on a series of 1,146 patients in whom the lumbosacral joints were compared mutually; he found asymmetry in 56 per cent. He was of the opinion that this asymmetry played a decisive part, because the strain on asymmetric articulation surfaces causes trophostatic changes. By examination of unexplicable scolioses in a great number of cases were found frontally placed, oblique articulation surfaces in the lumbosacral joints on the concave side of the scoliosis.

In 1,893 patients examined, the reviewer had found 139 (7.3 per cent) with unilateral sacralization. The most frequent change in 34 patients with unilaterally joined sacralization who suffered pain was oblique position of the vertebra; also there was deformity of the lumbosacral joint and finally changes in the intervertebral disk.

He looked upon the cleft in the lateral arch as a prespondylolisthetic condition. All of the 19 spondylolisthetic cases of the reviewer had stopped their slipping spontaneously. He also mentioned some cases of pseudospondylolisthesis (slipping in spite of the lack of cleft in the lateral arch), and maintained that these conditions were also dependent upon a defect in the arch, increased lordosis, and degeneration of the corresponding intervertebral disk. Further he mentioned briefly posterior slipping of the vertebral corpus, spina bifida occulta, hemispondylus, as well as ossification and calcification of the ligamentary apparatus.

**Sten Friberg,** of Stockholm, Sweden, had used Albee and Hibbs' method for operative treatment of spondylisthesis. In 3 cases, however, he had performed laparotomy and resection of the intervertebral disk with subsequent grafting of a piece of the iliac crest.

**R. Malmros,** of Copenhagen, Denmark, reported 7 cases of rupture of the intervertebral disk. He was of the opinion that this lesion might be traumatic, or might be caused by degeneration of the disk, or by both these factors combined.

The pain was the predominant symptom, but there occasionally also occurred myoclonus, tremor and atrophies.

Examination generally disclosed tenderness over the corresponding spinous process. Occasional elevation of the spinal fluid protein occurred. Ordinary roentgenologic examination was negative. The condition could not be diagnosed until a contrast medium was injected into the spinal canal.

**Carl Semb,** of Oslo, Norway, discussed clinical aspects of the lumbosacral lesions, particularly the symptom of radiating pain, which was an expression of reflex neuralgia and which had great diagnostic value. In the presence of lesions of the lumbar column radiating pain occurred in the anterior part of the femur corresponding to the lumbar segments. In lower lesions, iliosacral lesions for example, radiation to the posterior side of the femur and crus was usual. The necessity for cooperation with the neurologists was emphasized.

In two cases of bilateral sacralization Semb had performed a fixation or arthrodesis between the transverse process and massa lateralis by a grafted piece of the iliac crest. The patients became symptom free.

In two cases of painful articulation between the spinous processes of the lumbosacral region he had carried out resection of the spinous processes with good results.

**Nils Silfverskiøld,** of Stockholm, Sweden, discussed the importance of the shape of the sacrum based on 100 skeleton studies. With regard to the treatment of the sacralization and the spondylolisthesis, he strongly recommended conservative treatment. The sequence of the therapeutic measures should be as follows: (1) ordinary régime; (2) cast and exercise therapy; (3) operation.

As a supporting bandage in these lesions, he used a plaster cast for three to six weeks, then careful exercise therapy. The great majority of patients got rid of their symptoms by this treatment. Only as ultimate refuge should operation be resorted to.

**Fr. Roscher,** of Arendal, Norway, reported two cases of bilateral sacralization treated with resection of the transverse processes, resulting in cure.

**Hindahl,** of Denmark, also stressed the fact that conservative treatment should be tried in the first instance. In the presence of unilateral sacralization he preferred to carry out a fusion operation. He used Hibbs' method of spondylolisthesis.

A number of different papers were presented, in addition to the topics of discussion mentioned in the program.

**John Hellstrøm,** of Stockholm, Sweden, gave a paper on the incidence of persisting discomfort after cholecystectomy, which was based on 1,372 operated cases of cholelithiasis or cholecystitis. Follow-up examinations had been carried out in 1,041 patients, of which only 32.1 per cent were completely free of symptoms. Biliary colic persisted in 28.9 per cent, and gastrointestinal discomforts in 62.2 per cent. In women such discomforts persisted to a much greater extent than in men. Among those who had biliary colic after the operation were found 9 cases of common duct stone, necessitating another operation. Some of the gastrointestinal symptoms were explained by the achylia. The incidence of persistent discomfort was much less in patients who were operated upon after the first attack.

**K. K. Nygaard,** of Oslo, Norway, mentioned the postcholecystectomy syndrome and the postoperative strictures of the biliary duct. He drew attention to the investigations carried out by Walters, which demonstrated that morphine and pantopon caused a spasm in the sphincter of Oddi with resultant pain, while amyl nitrite and glyceryl-trinitrate relaxed the spasm.

**Ph. Sandblom,** of Ørebro, Sweden, had carried out investigations regarding Montprofit's cholecystojejunostomy, and he had found that this method was inferior to the gastrocholecystostomy.

**Sture Rødén,** of Stockholm, Sweden, had made a number of interesting "abdominal window" studies, and with the aid of a color film demonstrated the effect

of the peritonitis on the peristalsis. He further demonstrated that injection of hypertonic saline solution had a better and more lasting effect than peristalsis-inciting preparations.

**K. K. Nygaard** gave an account of a graphical method for the determination of the coagulability of the blood according to a photo-electric principle. A transportable coagelgraph constructed by the speaker was demonstrated.

**Einar Ljunggren,** of Sollefteå, Sweden, pointed out the similarity in the pyelogram of cystic pyelitis and of renal tuberculosis. He advised against operation on the roentgen diagnosis alone.

**Hans Hellmer,** of Lund, Sweden, treated the intravenous urography as a morphologic diagnostic procedure, and stressed the importance of carrying out increasing compression in order to obtain good pictures of the renal pelvis. He also recommended the use of softer rays and longer exposure to ensure that the ureters appeared clearly.

**C. Crafoord,** of Stockholm, Sweden, gave a paper on the diagnosis and treatment of the malignant tumors of the lung. He emphasized the importance of the roentgenologic examination—the bronchoscopy, and particularly the bronchography.

**C. Semb** maintained that the preliminary pneumothorax also belonged to the diagnostic facilities besides presenting advantages with a view to the subsequent operation. Semb treated in more detail three cases of intrathoracic tumors (fibroma of the lung, pericardial cyst, cancer of the lung—all removed), which had caused considerable diagnostic difficulties.

**Johan Holst** had operated upon 3 cases of cancer of the lung. One patient, in whom the upper lobe was removed, survived and was free from recurrence two years after the intervention.

**Einar Key,** of Stockholm, Sweden, mentioned 3 cases of cystic bronchial cavities, which had been confused previously with empyema. They had all been lobectomized.

**Johan Holst** gave a paper on lobectomy for bronchiectasis. He had performed 12 lobectomies and 1 pneumonectomy, mainly according to the technique of Brunn-Shenstone. The lesion was unilateral in 11 cases and bilateral in 1 case. Three patients had bronchiectatic cavities nearly the size of hen's eggs. All patients with unilateral lesion recovered—8 were symptomless; 2 are still under treatment.

**E. Perman,** of Stockholm, Sweden, gave an account of his thoracoplasties. He used a method of operation similar to that of Alexander-Maurer—large curved incision round the scapula. The arm on the diseased side was flexed alongside the head so as to obtain a less exposed position of the vascular and nerve plexus. Large pieces of the ribs were resected, particularly of the fourth and fifth ribs, with resection of the transverse processes. There was no apicolysis. The scapula was tipped under the ribs so as to be of service in the compression. He used painting with a solution of 4 per cent formalin in order to prevent regeneration of the periosteum. He had operated upon 40 patients with 2 deaths. All were operated upon in two stages.

**Sven Lundberg,** of Gothenburg, Sweden, performed his thoracoplasties under avertin anesthesia, in two stages: in the first stage anterior incision in the thorax with resection and apicolysis; three weeks later paravertebral resection from below upwards. The three upper ribs were totally removed. He spoke against resection of the transverse processes.

**Johan Holst** replied to Perman. If the pleura was thin, it was not advisable to destroy the periosteum because deficient regeneration may cause expansion of the lung. Resection of the transverse processes was superfluous, and in addition it caused extensive scoliosis.

**C. Semb** criticized the method used by Perman in that it did not give concentric collapse and that it necessitated needlessly great rib resections with danger of paradoxic respiration.

In his cases with extrafascial apicolysis Semb had a mortality of 3 per cent and collapse of the cavity in 90 per cent.

C. Semb gave a paper on the treatment of persistent cavities after previous thoracoplasties. He advised extrafascial apicolysis with resection of ribs correspondingly and, if necessary, resection of the transverse processes around the upward attachment of the apex of the lung in the second stage. The upper periosteal beds were mobilized posteriorly to enable them to collapse together with the apex and to fix the latter in its collapsed condition by regeneration of ribs. In 19 operated cases he had 1 postoperative death. In all of them except 2 cases collapse was obtained as well as freedom from bacilli.

**G. Nystrøm,** of Uppsala, Sweden, had experienced infection of the wound cavity in 20 per cent when using apicolysis, and he asked Semb how to avoid infection.

**C. Semb** pointed out that the apicolysis should not be made larger than required, that badly nourished intercostal musculature over the top of the lung had to be removed. Drainage, if at all necessary, should be of brief duration (twenty-four hours). Preliminary skin treatment for acne was important. In the presence of fistulas reoperation had to be carried out with excochleation and primary closure, and in some cases resection of the clavicle.

**Seved Ribbing,** of Uppsala, Sweden, had found, by histologic and roentgenologic examinations of the epiphysis of the lower femur in children from three to nine years of age, free bone islets close to the outline of the epiphysis in many cases. The localization of these bone nuclei corresponded to the place of predilection for osteochondritis dissecans at an older age and was assumed to be the constitutional factor in the etiology of this lesion.

**O. Aleman,** of Stockholm, Sweden, recorded a series of 91 fractures of the navicular bone, of which 79 cases were cross-fractures. Twenty-four of the latter were operated upon with removal of the smallest, or distal, fragment. The results of the operations were very good in 20 cases, good in 4 cases, and bad in no cases.

**C. Semb** drew attention to a few details of the nailing of fractures of the neck of the femur. He had constructed his own splint with a revolving crural attachment, which made it possible to obtain an effective inward rotation of the femur. After reposition by skeletal traction on this splint, the operation could be postponed until the general condition of the patient was satisfactory. The operation was performed with the patient in bed, and traction's being continued, by the Smith-Petersen/Johansson method. A sighting apparatus of own construction was used.

Of 101 operated cases subsequent displacement occurred in 4 cases only, of which the 3 were renailed with good results. There were 2 deaths; 1 from apoplexy.

**S. Johansson,** of Gothenburg, Sweden, maintained that the pronation did not play such an important rôle for the reposition. He himself used Braun's splint with traction on the tibia. He had operated upon 180 patients. The mortality was 10 per cent; the percentage of cure was 90 to 95 per cent.

S. Johansson also demonstrated 3 patients. In the 1, who had lost a thumb, he had prepared a new one by transplanting a tibial graft in the metacarpal bone and surrounding this with skin graft. The result was remarkably good.

**E. Platou,** of Oslo, Norway, gave a film demonstration of an extreme case of recurvatio genu congenitum, which made a four-legged creature of the patient. The operation here gave an excellent result with an erect walk.

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## MEETING OF THE ANESTHETISTS' TRAVEL CLUB, MONTREAL AND TORONTO, OCT. 18-23, 1937

EDWARD B. TUOHY, M.D., ROCHESTER, MINN.
*(From the Mayo Clinic)*

A MEETING of the Anesthetists' Travel Club was held in Montreal and Toronto; three days were spent in each city. **Dr. Wesley Bourne, Dr. C. C. Stewart,** and **Dr. Harold Griffith** were the hosts in Montreal and they demonstrated the methods of anesthesia which they currently use. The intratracheal method of general anesthesia, with cyclopropane as the anesthetic agent, is used predominantly. For certain types of operations, especially lower abdominal work, basal dosages of tribromethylalcohol (avertin) are used in conjunction with intratracheal administration of cyclopropane and oxygen.

The agent which is most commonly used for spinal anesthesia is nupercaine; a 1:1500 solution is employed, either by the Etherington-Wilson or the Howard Jones technique.

In the former method the patient is in the sitting position while the lumbar puncture is being made; and after the contemplated dose of the solution of nupercaine has been calculated, it is injected and the patient is maintained in the sitting position for a limited time, usually from fifteen to forty-five seconds, before being placed horizontally on the table. The Howard Jones method consists in performing spinal puncture, preferably with the patient lying on his side, and the height to which anesthesia is to progress is regulated by tipping the table so that the patient is held in varying degrees of the reverse Trendelenburg position. The doses of solution of nupercaine used in this technic, and in the Etherington-Wilson technic, are calculated on the same basis, the usual amount varying from 9 to 15 c.c.

**Dr. Griffith** uses cyclopropane for intratracheal anesthesia in operations on the eye, ear, nose and throat of children; he employs a silk woven catheter covered with rubber. The usual size of the catheters used in work with children varies from 24 to 30 French.

In connection with one of the obstetric departments in Montreal, it is the practice to collect blood from the placenta at the time of delivery. This blood is put in sterile containers, using sodium citrate as the anticoagulant. It is possible to obtain between 150 and 300 c.c. of blood in this manner and after the blood has been grouped it can be used for transfusions as is seen fit. It is noteworthy that the blood obtained from the placenta contains a great number of red blood corpuscles, frequently 7,000,000 per cubic centimeter. The method of keeping blood in the ice box for a limited time, not more than three weeks, also is used.

**Dr. C. H. Robson,** of Toronto, is employing intratracheal cyclopropane anesthesia with children, using the woven silk catheter previously mentioned. He is of the opinion that atropine should not be administered to children prior to anesthesia

Received for publication, Nov. 15, 1937.

by inhalation, because he feels that in not a few cases it causes a rise in temperature which is not attributable to some form of disease. The oral method of intubation for intratracheal anesthesia is preferred to the nasal method, because it is felt that in the nasal method there may be unnecessary trauma to the turbinates.

**Dr. H. J. Shields,** of Toronto, uses nupercaine for spinal anesthesia for upper abdominal surgical operations, employing the Howard Jones technique. He uses procaine in doses of from 250 to 300 mg. for thoracic operations. The total dose of procaine is dissolved in 10 to 12 c.c. of spinal fluid. Intravenous infusion is maintained throughout the course of the operation in order to combat any sudden fall in blood pressure. Dr. Shields has suggested that 50 c.c. of distilled water be injected intravenously in cases of headache following spinal anesthesia or in cases of any headache resulting from lumbar puncture. Why this procedure seems to be effective is not thoroughly understood.

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# REPORT OF THE MEETING OF THE FIFTH INTERNATIONAL CONGRESS OF RADIOLOGY IN CHICAGO, ILL., SEPT. 13-17, 1937

LEO G. RIGLER, M.D., MINNEAPOLIS, MINN.

*(From the Department of Radiology of the University of Minnesota)*

THE fifth congress of radiology of international scope was held in Chicago. The difficulty of summarizing the proceedings of a meeting which was held in nine sections and during which well over 200 papers were delivered in at least five languages can readily be imagined. The session was extraordinary both in its size and scope, and in the quality of the papers and exhibits. Only a few of the more important matters of general interest can be reported here.

**The Use of the Roentgen Rays in the Diagnosis and Treatment of Tumors of the Bladder** was presented by **George E. Pfahler,** of Philadelphia, Pa. He detailed his method of pneumocystography as a supplement to cystoscopy. Roentgen study after air injection permits better determination of the degree of infiltration of the bladder wall, the differentiation of papillomatous from infiltrating forms of carcinoma. Pfahler advocates roentgen therapy for inoperable tumors, reporting occasional startling cures. Combined intravesical destruction and irradiation is important. Cures of two to five years' duration were reported in 50 per cent of all the cases.

**Gösta Forssell,** of Stockholm, summarized his noteworthy researches on **The Rôle of the Autonomous Movements of the Gastrointestinal Mucous Membrane in Digestion.** He has demonstrated that the mucous membrane of the entire gastrointestinal tract moves independently of the muscle wall. He emphasized particularly that in this way recesses are created which are of vital importance in the digestive processes.

**Carl Sandström,** of Stockholm, described the **Diagnosis, Pathology, and Roentgen Treatment of Peritendinitis Calcarea,** usually called calcifying bursitis in this country. He reported cases of this type not only in the shoulder but also about practically all the joints of the extremities. Studies of the pathology show clearly that the calcification is secondary to necrotic changes in the tendons,

Received for publication, Nov. 26, 1937.

peritendinous connective tissue, periosteum, joint capsules, and ligaments. Roentgen ray treatment is highly effective, resulting both in the relief of symptoms and the disappearance of the calcium shadows.

A summary of the rôle of roentgenkymography in diagnosis was presented by **Pleikart Stumpf,** of Munich, the originator of this method. Kymography has two purposes: the fixation for study of movements which can also be observed more fleetingly in the fluoroscope; the observation of movements which occur so rapidly that they are not clearly seen on fluoroscopy, or so slowly that they are not noticed at all. He described his studies on the movements of the heart, lungs, thyroid gland enlargements, the gastrointestinal tract, and the upper urinary tract.

Motion pictures made from the image on the fluoroscopic screen were demonstrated by **Russell J. Reynolds,** of London, a pioneer in this field. He showed very effectively, in this way, the motions of swallowing, pulsations of the heart, movements of the diaphragms, lungs, and mediastinum. This method of demonstrating the movements of the stomach is much less effective under present technical conditions because of the short period during which the exposures may be made.

One of the most outstanding events of the Congress was a motion picture demonstration of the physiology of the heart in animals presented by **Werner Boehme,** of Rostock, Germany. Boehme first injects the animal with sufficient thorotrast to make the entire cardiovascular system, especially the cardiac chambers, brilliantly visible on fluoroscopy. Following this a second injection of iodized oil is made into the vein. Motion pictures at exceedingly great speeds then are made of the fluoroscopic image. The individual chambers of the heart can be seen and the droplets of oil are observed passing along the larger veins to enter the heart. In this manner many of the problems of cardiac physiology may be studied without opening the thorax or injuring the cardiovascular system.

**Nils Westermark,** of Stockholm, presented a very illuminating paper on **Bronchial Carcinoma, A Roentgen-Pathological Study.** He described the roentgen findings of very early carcinoma of the bronchus as a slight degree of localized atelectasis followed shortly by a more extensive area of emphysema. Repeated examinations will show increasing atelectasis following which bronchography will usually reveal a stenosed bronchus. From his studies Westermark believes the majority of bronchial carcinomas to originate in the smaller bronchi and to extend centrally at a later date. For this reason bronchoscopy may be ineffective as a diagnostic measure in the very early stages of the tumor.

**The Malignant Bronchial Stenosis, Bronchographic Aspect** presented by **Pedro L. Farinas,** of Havana, Cuba, described his studies using serial bronchography in the diagnosis of carcinoma of the bronchus. He attempts to distinguish between benign and malignant tumors of the bronchus and between the various types of malignant lesions by the character of the filling defect shown in the bronchogram. It is often difficult, however, to distinguish a tuberculous stenosis from a malignant one. The method is of particular value in the diagnosis of tumors of the smaller bronchi in which bronchoscopy is of little value.

**Ake Åkerlund,** of Stockholm, presented a review of his work on **Layer Formation in Vertical Cholecystography as an Aid in the Diagnosis of Small Gallstones.** He described the varying densities of gallbladder bile which cause a layering of the contrast medium when films are made with the patient standing. By making exposures during fluoroscopic observation, with pressure, in the upright position,

he was able to demonstrate small stones which were invisible in the ordinary cholecystograms. The position of the stones in relation to the gallbladder dye depends upon their specific gravity as compared to that of the bile and dye mixture. In some cases the stones form a layer of lessened density at the very tip of the fundus; in other cases they layer themselves in the middle or near the superior pole of the gallbladder. A similar study was presented by **Arnold Bernstein,** of Danzig. He emphasized particularly the demonstration of calcium bile in this same manner.

**Adaptability of the Mediastinum to Various Physiological and Pathological Conditions** was discussed by **John Alexander** and **C. B. Peirce,** of Ann Arbor, Mich. They described the changes in position and shape of the mediastinal structures which follow various normal and pathologic changes in the thorax.

**Cerebral Cystography and Cisternography** was presented by **Arthur Schueller,** of Vienna. He described in detail the roentgen findings in a variety of intracranial cysts, including the evidence derived from ventriculography with direct filling of the cysts with air. He also discussed the encephalographic demonstration of the changes in the cisternae of the brain which occur from various diseases. Schueller also advocated the intraspinal injection of iodized oil and the filling of the cisternae with the contrast medium by inversion of the patient.

**The Value of Encephalographic Studies Following Head Injuries** was presented by **J. T. Travers** of New York, N. Y. He described particularly cases of subdural hematoma, intracerebral hemorrhage, and brain atrophy, in which encephalography done three weeks or more after the injury clarified the nature of the intracranial lesion.

**W. J. Mixter,** of Boston, Mass., discussed **Rupture of the Intravertebral Disk** reviewing our present knowledge of this subject and detailing again the diagnostic criteria which have been described in previous papers. **Harry A. Olin,** of Chicago, Ill., described the general involvements of the intervertebral disk from injury or disease. He believes the disk may be readily injured by spinal puncture. Olin found extrusion of the nucleus pulposus into the vertebral body in 84 per cent of 50 cases of fracture of the spine.

**Hans H. Berg,** of Hamburg, presented his observations on **Gas Filling of the Bile Ducts.** He described numerous cases in which gas was demonstrated at the biliary duct system by roentgen examination. In one group this was due to internal biliary fistula from a variety of causes, chiefly the erosion of a gallstone. In the second group the gas resulted from infections of the biliary tract, cholangitis with and without abscess. Berg believes that more careful roentgen examination of the liver region in cases of undiagnosed abdominal conditions or complicated hepatic or gallbladder diseases will reveal many more of these cases and thus afford a clue to the nature of the lesion.

**J. A. Saralegui,** of Buenos Aires, detailed some more recent observations on cholangiography. He advocated a simple surgical procedure as a first stage operation in diseases of the gallbladder and biliary system; i.e., the insertion of a drainage tube into the fundus of the gallbladder. A week or so following, thorium dioxide sol (thorotrast 50 per cent) is injected and roentgen studies are made. Depending upon the roentgen findings, further surgical procedures of a more radical nature may be undertaken. By means of cholangiography he is able to demonstrate practically all of the normal and abnormal conditions which affect the biliary duct system and the gallbladder.

**B. R. Young** and **Michael Scott,** of Philadelphia, Pa., described the use of air as a contrast medium in the roentgen examination of the spinal cord. While not as accurate as iodized oil, it may be helpful in many cases and it does not have the deleterious effects attributed to the oil.

The general subjects of epiphyseolysis or separation of the proximal femoral epiphysis and aseptic necrosis of this epiphysis were discussed by **R. Pomeranz,** of New York, N. Y., and **A. Herzog,** of Czechoslovakia. The former described the findings in various stages based on 180 cases of slipped femoral epiphysis. He indicated the varying end-results of this lesion. Herzog related aseptic necrosis of the femoral neck to epiphyseolysis. He emphasized the points of distinction between aseptic necrosis, tuberculosis, and pyogenic infections and brought out that aseptic necrosis of the neck may follow a slipping of the epiphysis.

**Carl Wegelius,** of Helsingfors, presented data to show that urine is reabsorbed, probably from the kidney pelves. By roentgenographic means, he made volumetric determinations of the quantity of urine in the bladder. It appears that healthy individuals, whose bladders were greatly distended from drinking water, showed a recession in several hours of as much as 60 to 90 c.c. in the volume of the bladder without micturition.

Numerous papers were presented by a number of investigators on the relatively new procedure of tomography or planigraphy or laminagraphy, all of which detailed the uses of this method of roentgen examination in a variety of conditions. Essentially these procedures involve the production of roentgenograms which exhibit the structures in certain planes of the body with sharp detail while blurring out all the structures in all other planes. With a rather complex apparatus, in special instances, considerable improvement in roentgen diagnosis can be obtained. This is particularly true of such deep-seated structures as the sphenoid sinuses or in extensive disease of the lung. By the use of "subtraction" as described by **Zeidses Des Plantes,** of Utrecht, a similar result is obtained by a different method. The complexity of the procedure, together with the necessity for using numerous films, has militated against the general acceptance of the method.

**Albert Oppenheimer,** of Beirut, discussed **Acute Transient Intestinal Atony,** emphasizing the distention of the colon and even of the small bowel occurring during pyelography and renal colic. He believes this is due to inhibitory nervous impulses. It may occur as an independent transient phenomenon, accompanied by severe colicky pains, spontaneously subsiding in a few days. Most commonly it is secondary to other lesions such as duodenal ulcer, biliary colic, mesenteric thrombosis, etc.

**Philipp Sayhoun** and **Albert Oppenheimer** also presented new material on the roentgen diagnosis of appendicitis. They found stasis in the appendix to be due to degenerative changes in nerve ganglia with impairment of the peristaltic activity of the appendix. With these changes there usually occurs a leucocytic infiltration, probably inflammatory. A peculiar roentgen appearance, in the form of semilunar filling defects, may indicate an inflammatory edema of the mucosa, an acute phase of the appendiceal stasis.

The Janeway Lecture of the American Radium Society was delivered by **Douglas Quick,** of New York, N. Y., on **Carcinoma of the Larynx.** He reviewed the history of the treatment of this disease. He has abandoned the terms intrinsic and extrinsic, but substitutes for them carcinoma of the larynx proper

(intrinsic) and carcinoma of the hypopharynx (extrinsic). Quick believes that the results achieved with high voltage x-rays during the past five years make total laryngectomy an obsolete procedure. The most important features of the application of radiation therapy are daringly intensive radiation and individualization of the case.

**Henri Coutard,** of Paris, also presented the results of roentgentherapy of cancer of the larynx after five and ten years of observation. The differences in results are much more dependent on the histologic type than on the extent of the lesion. Those of the cutaneous type, which are highly differentiated and most infiltrative, are least responsive, while the epitheliomas of the mucous membrane type are most readily cured. In the latter, various types of treatment have been successful. In the former, changes in methods of treatment have been of little avail. Coutard reported 27 per cent of all his cases treated from 1921 to 1932 cured for a five-year period. The cures have been maintained, on the whole, for a ten-year period.

**Hans Holfelder,** of Frankfort, presented a method for evaluating the results of radiation therapy. In general, he reviewed the information such as the nature of the tumor, the quality and quantity of the irradiation, the method of application, etc., and suggested exact methods for recording these data.

**Hermann Holthusen,** of Hamburg, reviewed his own well-known work on the relationship of the biologic nature of tissues to their reaction to irradiation.

**The League of Nations' Work on Uniform Statistical Presentation of Results in Radiotherapy of Uterine Cancer** was presented by **James Heyman,** of Stockholm. The report of this committee concerned itself with a proper anatomic classification of cases, with recommendations for proper statistical methods and with procedures for calculating results.

**Fred Taussig,** of St. Louis, advised the use of iliac lymphadenectomy together with irradiation in the treatment of cervical cancer. He reported improved results with this method.

**Auguste Gunsett,** of Strasbourg, reported his experiments with the use of 520 kv. as compared to 200 kv. x-rays. He is firmly convinced of the superiority of the higher voltages. **S. G. Mudd, C. K. Emery,** and **L. M. Levi,** of Pasadena, Calif., also reported more encouraging results in the treatment of various cancers when supervoltage x-rays were employed. **R. S. Stone,** of San Francisco, Calif., discussed his experiments which appear to demonstrate that skin reactions were not less with 1000 kv. x-rays than with 200 kv. x-rays. From the standpoint of skin tolerance, super voltage is only of advantage in extremely thick parts or when cross-fire is not used. **T. Leucutia,** of Detroit, Mich., reporting on a comparison of clinical results over a three-year period using 500 kv. and 200 kv. therapy, found that the higher voltages were superior only in those cases in which the carcinoma is very deep seated or has infiltrated surrounding tissues to a considerable degree. The outstanding example of this improved response is in the frozen pelvis due to carcinomatous infiltration from carcinoma of the uterine cervix.

Further evidence favoring the fractional method of irradiation was brought out by **Carl Fried,** of Breslau. He emphasized the use of this method particularly in inoperable tumors and reported surprisingly good results in certain cases of gastric cancer, brain tumors, and advanced carcinoma of the breast and bladder.

**Wm. E. Howes,** of Brooklyn, N. Y., and **G. T. Pack** and **Gordon McNeer,** of New York, N. Y., likewise recommend greater use of radiation therapy in the inoperable cases of carcinoma of the stomach.

**Alexander Brunschwig,** of Chicago, Ill., reported his observations on the histology at the site of benign giant cell tumors several years after conservative treatment, such as irradiation or curettage. There is an unusual slowness of reossification in such tumors so that roentgenograms several years after treatment may show little change from the original appearance in spite of the fact that no tumor remains.

**Congo Red and Liver Therapy in Roentgen Sickness** was discussed by **Isidore Arons** and **Boris Sokoloff,** of New York, N. Y. They found that Congo red and liver combined were of practical value in combating both the roentgen sickness and the anemia which often follow irradiation. Incidentally, they discovered that these two substances, in themselves, exercised a pronounced inhibiting effect on the growth of mouse sarcoma.

An extensive symposium on the radiation therapy of carcinoma of the breast was held, some eight papers being presented. The essayists discussed various phases of this problem, but there was general agreement that a combination of surgery and irradiation is the best method of treatment. Good results were reported with the use of preoperative as well as postoperative irradiation Simple mastectomy with postoperative x-ray therapy, in one series of cases, seemed to afford a relatively high percentage of cures.

An important review of irradiation therapy of cancer was given by **Hans R. Schinz,** of Zurich, who reported his observations over a seventeen-year period.

The treatment of acute pneumonia, particularly of the lobar type, by x-radiation was reported on by **Eugene Powell** of Temple, Tex., and **Carl Fried,** of Breslau. The latter presented experimental evidence to support the clinical experience of the rapid resolution of both lobar and postoperative pneumonia. **M. Berck,** of New York, N. Y., again reviewed the results of roentgen therapy for bronchiectasis. He believes that moderately large doses of x-rays present a feasible and successful treatment for many cases of chronic secreting bronchiectasis.

Most of the papers presented in the sections on radiobiology and radiation physics were of a highly technical nature. There were a number of presentations detailing investigations on the effects of neutrons on biologic materials.

**John H. Laurence, Paul C. Aebersold,** and **Raymond E. Zirkle,** of Berkeley, Calif., reported the varying effects of neutrons on different substances leading to the possibility that this form of radiation may be specifically more effective than radium or x-rays on certain neoplasms.

**J. Gershon-Cohen, Harry Shay, David R. Meranze,** and **Samuel S. Fels,** of Philadelphia, Pa., reported their observations on the irradiation of the thymus in rats. The atrophy produced seemed to have a definite relationship to general growth, skeletal development, and particularly to development of the genital system.

Numerous other papers of great interest to the radiologist and the physicist, but of less general interest, were presented.

# Book Reviews

**Operative Surgery, the Ear, Air Passages and Neck.** By Dr. Martin Kirschner (with the collaboration of A. Lautenschläger and O. Kleinschmidt). Authorized translation by I. S. Ravdin and George M. Coates. Pp. 528, with 460 illustrations. Philadelphia and London, 1937, J. B. Lippincott Company. $10.

This, the third volume in the operative surgery series of Professor Martin Kirschner, of Heidelberg, is worthy of the distinction of appearing on the shelf beside its two illustrious predecessors. This volume appears in two parts; the first relates to operations on the ear, the nose and its appendages, the pharynx, larynx, trachea, and bronchi. This section is written by Professor Lautenschläger, of Berlin, and is edited and translated by Dr. George M. Coates, of Philadelphia. Part Two concerns operations on the esophagus and other structures of the neck and is written by Professor Kleinschmidt, of Wiesbaden, and is edited and translated by Dr. I. S. Ravdin, of Philadelphia, who also sponsored the appearance of the first two volumes in English.

The approach to the description of operative procedures is distinctly anatomic. The influence of years of contact with cadaver surgery in the teaching of applied surgical anatomy to medical students, an exercise to which every academic German surgeon is thoroughly exposed, is immediately apparent. The anatomic plan of operation so well elucidated by the authors is worthy of careful study. Physiologic considerations relating to the operations described, however, are often totally ignored by the writers. In the section on the neck, some of the obvious omissions have been repaired in part by the insertion of short pertinent sentences by the editor.

The illustrations, of which there are a large number, are beautifully done in color and add much to the effectiveness of the descriptions. How often American authors have occasion to be envious of their continental colleagues whose publishers permit them to use illustrations in color so generously.

A serious omission, the reviewer feels, is failure to append a satisfactory bibliography. Scores of names (largely German) are cited throughout the volume, but where these references are to be found is not intimated. The usefulness of the volume would have been increased several fold to the critical student of surgery by the proper insertion of suitable references.

The volume can be whole-heartedly recommended to any serious student of surgery having an interest in the subject matter.

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**Surgical Treatment.** By James Peter Warbasse and Calvin Mason Smyth, Jr. Third vol. Ed. 2. Pp. 906, vol. I; 782, vol. II; 798, vol. III. Philadelphia, 1937, W. B. Saunders Company. $35.

Francis Bacon, in his day, took all knowledge for his province. With the development of science—which Oliver Wendell Holmes defined as the topography of ignorance—men have become less bold in their excursions into diverse branches of learning. No man longer essays to encompass the entire field of medical knowledge. Surgery, too, has become so broad that no one man's or even two men's knowledge extends completely into its numerous ramifications. In this weakness lies the fundamental defect of these volumes.

Jacobsen and Kocher, profound students of surgery in their day, were able to write, unaided, works on operative surgery which their contemporaries and even men of our generation have zealously studied. Jacobsen's *Operations of Surgery* and Kocher's *Operative Surgery* became the *vade mecum* of Anglo-Saxon and Teutonic surgeons. The authors of those volumes directed their efforts to help instruct the best informed surgeons. In consequence, they fathered texts which reached an unusually large audience.

The authors of these three volumes on surgical treatment have essayed to discuss both nonoperative and operative treatment of surgical disorders. They have levelled their effort undoubtedly at the general practitioner who will find contained in these volumes a surprising mass of useful information. The experienced surgeon will find in them much to commend and much with which he will disagree or which he will feel inclined to criticize. He will miss particularly the critical scholarly attitude which he is wont to expect in a work of this magnitude. He will note the absence of references—a serious omission in the eyes of the inquisitive and fact-seeking surgeon. He will find statements once contained in texts that are now obsolescent. It is to be hoped that when a third edition of these volumes is written many of its inaccuracies will be corrected by the inclusion of more authors whose fused efforts will constitute a more scientific and authoritative treatise. The wide audience of American surgeons is deserving of the best conjoint effort of a strong medical publishing house and alert and experienced surgeons possessed of a scientific and scholarly interest. Volumes which are sufficiently authoritative to instruct the best informed of surgeons are also the most valuable and the safest sources of information for the "occasional surgeon."

One of the best chapters of these volumes deals with amputations. A large number of worth-while practical suggestions constitute an important feature of the volumes, which are profusely and well illustrated. The final chapter deals with the "economic and social aspects of surgical treatment" and contains a plea for a wider general culture on the part of the surgeon. Each volume has its index; an additional small fourth volume contains a good subject index of all the volumes.

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**Synopsis of Digestive Diseases.** By John L. Kantor. Pp. 206, with 40 illustrations. St. Louis, 1937, The C. V. Mosby Company. $3.50.

Within the restrictions necessarily imposed upon presentations in synopsis form, the author reviews gastroenterologic diseases, including most of the important recent contributions to this field of medicine. The digestive disorders are broadly divided into those due to constitutional digestive inferiority, those due to acquired digestive disease, and those due to extradigestive disease. In his presentation of the various gastrointestinal lesions the author discusses the etiology, the pathology, the altered physiology, and the clinical and special diagnostic methods; following which he either gives detailed descriptions of the dietary or other medical treatment or indicates briefly the surgical procedure which may be indicated. From the standpoint of interest and value to the reader, this book might be used as a review course or even as a source of quick reference, especially for general practitioners.